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DEPT. OF TRANSPORTATION DOCKETS

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BEFORE THE
DEPARTMENT OF TRANSPORTATION

In the Matter of: **Procedures for Transportation Workplace Drug and Alcohol Testing Programs**	)	**Docket No. OST-2003-15245** -10 **RIN 2105-AD26**

COMMENTS OF
THE AIR LINE PILOTS ASSOCIATION
AND
TRANSPORTATION TRADES DEPARTMENT, AFL-CIO

The Air Line Pilots Association ("ALPA") is the principal labor union representing the nation's commercial pilots. It represents more than 66,000 pilots at 42 airlines in the United States and Canada. The Transportation Trades Department of the AFL-CIO ("TTD") is the transportation umbrella organization for the AFL-CIO and is comprised of 35 affiliated unions, many of whom represent employees subject to DOT regulated drug testing.[1] These comments are filed on behalf of ALPA and TTD.

We maintain our objections to validity testing and incorporate by reference our prior comments on the issues related to such testing. (See attachment B, incorporated by reference herein.) We are glad to see, however, that the Department of Transportation is finally recognizing that its creatinine cutoff level for considering a urine sample to be "substituted" is not low enough, and inappropriately treats the small

[1] The unions represented by TTD are listed in Attachment A to these Comments.

percentage of individuals who produce ultra-dilute urine as rule violators. While the approach taken in the interim regulations is a move in the right direction, further modifications to the regulations are necessary to address and prevent harm to employees whose creatinine levels are at or below 5 mg/dL, the regulatory "substitution" cutoff.

In this interim rule, DOT acknowledges that individuals have come to its attention who produced urine specimens with creatinine at or below 5 mg/dL and were reported as having "substituted" their samples under the rule. Such individuals were generally otherwise healthy persons who naturally produce ultra-dilute urine, with no wrongdoing on their part. DOT also acknowledges the views of scientific and medical experts in relevant fields that the standard of 5 mg/dL may not be appropriate.

In recognition of these facts, the amendments to the rule incorporate an "interim" measure of having the Medical Review Officer ("MRO") report specimens with creatinine levels greater than or equal to 2 mg/dL but less than or equal to 5 mg/dL as "dilute" and require the employee to submit to an immediate directly observed urine collection. While this change is progress, it does not correct the problematic regulatory standard, and regulatory language ascribing wrongdoing to the employee. To the contrary, DOT asserts that it is *not changing* the existing substitution criteria contained in 49 C.F.R. Section 40.93. Moreover, individuals whose specimens were reported as "substituted" prior to the effective date of the amendment are still being treated by their employers as having substituted their samples.

As shown by the experience of individuals affected by these rules and confirmed by the opinions of the scientific community, the standard in DOT's regulations which characterizes employees' urine as "substituted" merely because it has creatinine at or below 5 mg/dL (along with specific gravity that is less than or equal to 1.001 or greater than or equal to 1.020) is based on the erroneous assumption that such levels cannot be human urine. This assumption, reflected in the notice of proposed rulemaking, has been consistently challenged and refuted in comments submitted, and is now acknowledged by DOT to be erroneous. DOT should act promptly to correct this error and ameliorate the situations of employees adversely affected by this regulatory provision.

As DOT and HHS are well aware, this standard has been applied to individuals who naturally produce ultra-dilute urine with low creatinine levels, and, as a result of having their urine deemed "substituted," were terminated from their jobs, and spent much time and expense procuring medical and scientific evidence to exonerate themselves. The application of this standard has caused tremendous personal and financial hardship to those individuals who, while engaging in no misconduct, were branded wrongdoers and bore the burden of proving their innocence. In light of the evidence that some individuals do produce ultra-dilute urine with low levels of creatinine, DOT should modify the regulations to use the term "ultra-dilute" urine instead of "substituted," and such change should be retroactively applied. To correct the harm done to innocent employees and to prevent any such future harm, the regulations should include a clear statement that individuals whose urine specimens are (or previously were) within the new, intermediate level of between 2 mg/dL and 5 mg/dL creatinine are *not* to be treated as having "substituted" their samples.

These corrections to the regulations should be made immediately. We are troubled by DOT's reluctance to change the regulatory standard and its statement that the process in which it is engaging related to the issues involving substitution "may take considerable time." 68 Fed. Reg. 31624 (May 28, 2003). In our view, DOT acted precipitously and inappropriately when it regulated a standard of urine dilution without sufficient scientific data to support its cutoff levels. In contrast to DOT's imposition of the "substitution" cutoff levels in its revised regulations published in December 2000, HHS sought and received comments through October 21, 2001 on proposed scientific guidelines pertaining to validity testing. Nonetheless, to date it has failed to issue any final regulations. We agree that careful consideration of relevant scientific and medical data is appropriate but such review should take place *before* such standards are implemented. Accordingly, should further study be undertaken, such review should continue without ongoing jeopardy to employees. We urge that the DOT regulations be immediately amended to address these issues.

Finally, it should be recognized that the levels of creatinine and specific gravity *reported* may not accurately reflect the true levels of creatinine and specific gravity of the urine specimen. As has been demonstrated, laboratory error can account for erroneous readings. The DOT rules should be amended to provide a process by which readings resulting from faulty laboratory work – as opposed to "a legitimate medical explanation" – can be identified and addressed. We have previously raised our concerns about the need for employees and their unions to have an inexpensive and expeditious means to gain access to information necessary to uncover such laboratory error, in order to show employee innocence, as well as to protect the integrity of the system. See comments in Attachment B, Tab 3 (submitted to DOT June 14, 2001). We renew our request that DOT consider these comments and the important functions served by providing greater access to information provisions.

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Date: August 26, 2003

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The following labor organizations are members of and represented by the TTD:

Air Line Pilots Association
Amalgamated Transit Union
American Federation of State, County and Municipal Employees
American Federation of Teachers
Association of Flight Attendants
American Train Dispatchers Department
Brotherhood of Locomotive Engineers
Brotherhood of Maintenance of Way Employes
Brotherhood of Railroad Signalmen
Communications Workers of America
Hotel Employees and Restaurant Employees Union
International Association of Fire Fighters
International Association of Machinists and Aerospace Workers
International Brotherhood of Boilermakers, Blacksmiths, Forgers and Helpers
International Brotherhood of Electrical Workers
International Brotherhood of Teamsters
International Federation of Professional and Technical Engineers
International Longshoremen's Association
International Longshore and Warehouse Union
International Organization of Masters, Mates & Pilots, ILA
International Union of Operating Engineers
Laborers' International Union of North America
Marine Engineers Beneficial Association
National Air Traffic Controllers Association
National Association of Letter Carriers
National Federation of Public and Private Employees
Office and Professional Employees International Union
Professional Airways Systems Specialists
Retail, Wholesale and Department Store Union
Service Employees International Union
Sheet Metal Workers International Association
Transportation • Communications International Union
Transport Workers Union of America
United Mine Workers of America
United Steelworkers of America

DOCKET NO. OST-2003-15245
ATTACHMENT A TO COMMENTS OF AIR LINE PILOTS ASS'N AND TRANSPORTATION TRADES DEPARTMENT, AFL-CIO

July 2003

Transportation Trades Department, AFL-CIO

BEFORE THE
DEPARTMENT OF HEALTH AND HUMAN SERVICES

Substance Abuse and Mental Health Services Administration	)	
In the Matter of:	)	
MANDATORY GUIDELINES FOR WORPLACE DRUG TESTING PROGRAMS	)	FR Doc. 01-20945

COMMENTS OF THE AIR LINE PILOTS ASSOCIATION AND THE TRANSPORTATION TRADES DEPARTMENT OF THE AFL-CIO

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DOCKET NO. OST-2003-15245
ATTACHMENT B TO COMMENTS OF AIR LINE PILOTS ASS'N AND TRANSPORTATION TRADES DEPARTMENT, AFL-CIO

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BEFORE THE
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COMMENTS OF THE AIR LINE PILOTS ASSOCIATION AND THE TRANSPORTATION TRADES DEPARTMENT OF THE AFL-CIO

Introduction and Summary

The Air Line Pilots Association ("ALPA") is the principal labor union representing the nation's commercial pilots. It represents more than 67,000 pilots at 47 airlines in the United States and Canada. The Transportation Trades Department of the AFL-CIO ("TTD") is an organization of the AFL-CIO comprised of 33 unions that represent millions of employees in transportation industries.[1] Some of the unions in TTD also represent federal employees. These affiliated unions represent employees subject to DOT regulated drug testing (governed by 49 CFR Part 40) as well as federal agency drug testing, all of whom are affected by the proposed regulations. ALPA submits these comments on its own behalf and on behalf of TTD in response to the above-captioned

[1] The unions represented by TTD are listed in attachment 1 to these Comments.

Notice of Proposed Rulemaking ("NPRM"). Mandatory Guidelines for Federal Workplace Drug Testing Programs, 66 Fed. Reg. 43,876 (August 21, 2001).

ALPA and TTD maintain their opposition to mandatory "validity" testing in the manner in which HHS and DOT seek to implement it. While we appreciate the improvements that have been made to the procedures, we are still concerned about the lack of certain fundamental safeguards, the failure to meet acceptable scientific standards and the continued risk of innocent employees being improperly deemed to be rule violators.

Experience over the past few years has shown that innocent employees have been falsely reported to have adulterated or substituted their urine samples, and have been terminated from their jobs as a result. Such reports have resulted both from laboratory error – including egregious misconduct and failing to comply with applicable quality control standards – and from a small number of otherwise healthy individuals who produce ultra-dilute urine and who have had creatinine and specific gravity reported below the regulatory cutoff levels. The dire consequences to an employee of being reported as having tampered with his or her urine specimen necessitates that any validity testing protect such innocent individuals as well as meet the highest forensic and due process standards.

I. VALIDITY TESTING

Although HHS cites figures of failed validity tests over the past few years, it fails to distinguish between tests of applicants versus those of actual employees. There is a significant difference in test results between the two categories. From what we have seen, and what experienced collectors have reported, the overwhelming number of problematic test results has been on preemployment tests – not those of current employees.

Moreover, the percentage of specimens reportedly "adulterated" or "substituted" is negligible, at worst. See 66 Fed. Reg. at 43,877 (allegedly 6,440 adulterated specimens and 2,821 "substituted" specimens out of 13 million specimens). If these numbers are adjusted to consider tests of only current employees, the problematic results would be virtually nil.

It should also be noted that "Bayes Theorem" postulates that when the prevalence of a condition being tested is quite low, the probability that a particular result is true is greatly decreased. See R.S. Galen and S.R. Gambino, Beyond Normality: The Predictive Value and Efficiency of Medical Diagnoses (1975). This respected theorem has shown the statistical risks of increased false results in a population, recognizing that all testing procedures are less than 100% perfect. Based on the HHS figures, the extremely low prevalence of "adulterated" results (.049%) and the even lower prevalence of "substituted" results (.021%), would cause the number of false positives to be much greater than the number of true positive readings. Id.

We also submit that there is the least justification and the greatest concern about the so-called "substitution" testing. Even considering reported results that include applicants, the number of "substituted" specimens is far, far less than reported "adulterants." Id. Moreover, as we show below, the "substitution" cut-offs include otherwise innocent employees, as shown by actual experience and the existing scientific studies.

And finally, while improvements have been made to the testing for adulterants – such as some requirement for "true" confirmation tests – such protections remain wholly lacking for creatinine and specific gravity tests. In sum, while we believe the government has failed to produce evidence justifying any mandatory validity testing, the deficiencies involved in the required testing for urine dilution overwhelmingly mandate a serious reconsideration of this aspect of the proposed regulations.

A. The Accuracy Of Any Required Or Permitted Validity Test Must Be Guaranteed.

1. Any Screening Tests To Detect Adulterants Or Measure Urine Dilution Should Be Permitted Only After The Accuracy And Reliability Of Such Tests Have Been Determined, A Process Accomplished By FDA Clearance Or Approval.

The proposed screening tests are gross tools that have been approved or cleared largely for clinical purposes but do not have the same degree of precision as is necessary for workplace employee testing. Whether a patient's urine has specific gravity of 1.001 or 1.002 is of little consequence in the context of patient care. Likewise, a difference between 5 mg/dL and 6 mg/dL of creatinine is not clinically significant. Under the mandatory validity testing program, however, such differences determine whether an individual's livelihood is terminated. Thus, while these tests may be sufficiently accurate or reliable for clinical care of patients, they do not meet the requisite forensic standards for a government imposed employee testing program.

FDA review can address some of these concerns. Such review is especially important for validity tests for a number of reasons. First, the proposed regulations allow final results – results upon which an employee's career will depend – to be based on screening tests alone. Accordingly, it is all the more important to identify the error rate of the screening tests. Second, there are no restrictions or limitations on the particular screens or assays that may be used. Unlike NHTSA approval of alcohol testing devices or HHS certification of laboratories, there is no such government certification of these tests. Nor is information about the content or composition of the reagents used in the screening tests necessarily available to the public without FDA review. Such information is essential in order to evaluate and eliminate alternative explanations or causes of results reported as positive. Such information is also necessary to enable meaningful MRO review.

The FDA plays a vital role in reviewing commercial tests involving health, food and drugs, as well as commercial tests sold for diagnostic purposes. The process by which the FDA clears or approves such tests involves having the manufacturer prove that the test accurately and reliably does what it purports to do. Such review identifies the diagnostic sensitivity (true positive rate), diagnostic specificity (true negative rate), and the predictive value of the detection of the compound (or property) being tested. It also looks at the chemical or scientific basis of the test, identifies the reagents, and inspects the manufacturing process to verify the components of the test. These review processes identify potential causes of false positive and false negative test results. The immunoassays used to screen for drugs and drug metabolites under the DOT drug testing program have long been subject to such FDA oversight.[2]

[2] This requirement was previously contained in 14 C.F.R. Section 40.29(e). See 54 Fed. Reg. 49,854, 49,872 (Dec. 1, 1989). It was removed when the regulations were revised in December 2000. See 14 CFR Section 40.87(a), replacing 40.29(e). See also Section 2.4(e)(1) adopted in the HHS Guidelines. 53 Fed. Reg. 11,970, 11,983 (Apr. 11, 1988).

The FDA oversight process identifies the error rate of a test or device, when it is used for the purpose for which the FDA is reviewing it. While some of the screening tests used for validity testing may have been cleared or approved for other purposes – such as to identify bacterial infections, or to test renal function – they have not been assessed for their ability to identify adulterants, validate urine at the cutoff levels, or even measure creatinine in urine. Such FDA review would result in the identification of the predictive probabilities of the tests for the variable being tested for, and ultimately determine the error rate of the test being used. In sum, FDA review is an extremely valuable tool for assuring a high standard for employee testing, and a vital means of obtaining key information about the applicable tests. Such review should be mandated by the regulations.

2. It Is Essential That Any Required Validity Test Be Confirmed With A Second Test That Utilizes A Different Physical Or Chemical Property Than The Initial Test.

As ALPA expressed in its Comments to Docket No. 0ST-99-6578 (Part 40 NPRM), it is a fundamental principle in forensic toxicology that at least two different analytical techniques must be used in order to assure an accurate test result. See attachment 2 at 6, citing J. J. Reese, American Academy of Forensic Sciences Policies on Confirmation; R.H. Cravey and R.C. Baselt, Introduction to Forensic Toxicology (Biomedical Publications, Davis CA 1981); B. Levine, Principles of Forensic Toxicology (1999); American Academy of Forensic Science/Society of Forensic Toxicologists Forensic Toxicology Guidelines. Underlying this tenet is recognition that no test is 100% accurate; therefore the probability of a correct result is increased when the result is confirmed using a different methodology. Or, put another way, the consistent, corroborative findings of independent tests of the same value or fact increases the probability that the finding is true. The failure to require a confirmation test that utilizes a different testing methodology is a serious procedural flaw, which can cause grossly inaccurate test results.

This significant failing is not cured by repeating the same test on two different aliquots because the second test is not independent and thus would be subject to the same errors and interferences as the first. For example, if there is interference with the screening test – such as from medication or menstrual blood in the urine – such interference would be repeated if the same procedure, method, and/or instrument is used again, regardless of the nature of the testing method, and the number of times it is used.

For this reason, to increase the predictive value of a test to acceptable levels, at least two independent procedures must agree on the result. To be independent, they must be carried out on two different aliquots and they must be based on different physical or chemical properties of the analyte. See e.g., V.R. Spiehler et al., Confirmation and certainty intoxicological screening, Clin. Chem. 34:1535-39 (1988); M. Zweig et al., NCCLS GP 10P, Assessment of clinical sensitivity and specificity of laboratory tests, National Committee for Clinical Laboratory Standards, Villanova, PA (1987); M.H. Zweig et al., Receiver-Operating Characteristic (ROC) plots: a fundamental evaluation tool in clinical medicine, Clin. Chem. 39:561-77 (1993).

The proposed regulations state that such confirmation testing shall be used for adulterants, but then follow that statement with an exception that eviscerates the protection. The two sections of the proposed regulations governing testing for adulterants state: "A confirmatory test . . . shall use a different analytical principle or chemical reaction than that used for the initial test unless a recognized reference method is used for both the initial and confirmatory test" (emphasis added). See proposed sections 2.5(h)(2) and (j)(2). 66 Fed. Reg. at 43,881-82. This loophole eliminates a true confirmation test if a "recognized reference method" is used.

The term "recognized reference method" is not defined in the regulations and could be subject to various interpretations. But regardless of what testing method is used and how accurate and reliable it is supposed to be, repeating the same test cannot afford the protection that a truly independent test can. A confirmation test is not required because the initial tests are unreliable; all tests used by NLCP laboratories are, or should be, reliable. A confirmation test is required to increase the probability that the result is a true positive or true negative to a level of probability sufficiently certain to stake a person's career upon that reported result.

The proposed rule also states "In some cases both initial and confirmatory validity tests may use the same procedure, instrument or method." See Subpart B, ¶10. (d)(1), 66 Fed. Reg. 43,881. Like the rigorous standards required by law when testing employees' urine samples for the presence of illegal drugs, so too should such equally stringent requirements apply to validity tests which can be similarly career-ending. The increased assurance of true results that comes from confirmation tests should apply to any tests used to measure urine dilution. Accordingly, we strongly urge that these exceptions and loopholes be removed from the rules.

The same need for confirmation exists with respect to tests of creatinine and specific gravity. DOT sought to distinguish these tests claiming there was no need to confirm such results with a test using a different physical or chemical property because creatinine and specific gravity are unlike the "chemically complex substances" that comprise illegal drugs. See 65 Fed. Reg. 79,462, 79,480 (Dec. 19, 2000).[3] DOT also claimed that because creatinine is expected to be found in urine, that fact somehow makes confirmation testing superfluous. Id. These facts have no relevance to the rationale and need for confirmation testing.

The pertinent issue is not the chemical complexity of creatinine in relation to the chemical complexity of other substances expected to be found in urine, as DOT seems to be saying. What is significant is that simple colorimetric tests, such as those for creatinine, may falsely report a positive result due to various reasons (such as a machine pipette failure, a reagent reaction problem, etc.). Any such problems would not be cured by repeating the same test.

It is also incorrect, as DOT claimed, that an initial creatinine validity test is analogous to a confirmation drug test. Id. Neither from a chemical, scientific, analytical or probability standpoint, does an initial creatinine test accomplish the same goals as a drug confirmation test. Nor does the mere fact that a screening test produces a "quantified" result increase the probability that the results are true – as does an independent confirmation test. How "chemically complex" creatinine is, and the fact that some levels are normally expected to be in urine, have no relation to the function and

[3] In fact, creatinine is more chemically complex than methamphetamine.

value of an independent creatinine confirmation test. The same is true for specific gravity tests.[4]

Nor is there any practical reason to exempt these validity tests from higher scientific standards than other validity tests. Creatinine can be confirmed by chromatographic tests, which are commonly performed by laboratories and readily available. If initial specific gravity tests are done using refractomers, confirmation tests can be done either with a hydrometer or with a balance. These methods are easily done and likewise, readily available. There is simply no justification for exempting any mandated testing, with potentially career-ending consequences, from standards less protective than those applicable to drug testing.

3. The Non-Specific Testing Proposed For Oxidizing Adulterants Fails To Meet Scientific Standards.

In contrast to the testing proposed for specific adulterants, creatinine and specific gravity, HHS is seeking to allow tests for other unidentified "oxidizing" agents that, if present in a sample at any detectable level, requires the test to be reported as an "invalid specimen" – a category that implies employee misconduct and one which subjects that person to directly observed testing. While we understand that HHS is concerned about

[4] Following the creatinine test with a test for specific gravity does not constitute a "true" confirmation test either. Each test is measuring a different property and is subject to its own variations in precision and accuracy. Moreover, specific gravity is neither a reliable confirmation of a creatinine level nor a suitably independent measure of urine diluteness to meet forensic standards. See Spiehler Report (Attachment 1 at attachment 1, p.9) citing W.V.R. Vieweg et al., Psychogenic Polydipsia and Water Intoxication-Concepts That Have Failed. Biol. Psychiatry 20:1308-20 (1985); S.B. Needleman et al., Creatinine Analysis In Single Collection Urine Specimens. J. For. Sci. 37:1125-33 (1992). The variable correlation between specific gravity and creatinine in individual patients has been found to range from 0.618 to 0.935. Id.

identifying new adulterants, the approach suggested has serious problems and should not be adopted.

First, there are no standards governing the types of tests that may (and may not) be used for such general adulterant testing. It is essential to know the chemical composition of any such tests because that will determine what other compounds will react positively to the testing reagent and could cause "false positives." F. Urry et al., Nitrite adulteration of workplace urine drug-testing specimens. Sources and associated concentrations of nitrite in urine and distinction between natural source and adulteration. Journal of Analytic Toxicology 22:89-95 (1998).

It is also important to know the chemical composition of these tests in order to know what properties of the specimen might interfere with the tests. For example, nitrites are detected through a color-producing reagent. Blood in the urine can cause that test to report false positives since the color of the blood can falsely indicate a "positive" result. There are also many oxidants that occur naturally in the environment and in humans, such as blood, feces, bacteria, iron, etc. Knowledge of the basis of a test's oxidizing reaction is essential so that MROs, affected individuals and their representatives can identify the true causes of any such reported positive.

Any such tests should also be subject to the same rigorous standards as those for other validity and drug tests. The accuracy and reliability of the testing methodology should be identified and reviewed before employees suffer any actions as a result of those test results. Additionally, before any test reaction is treated as a true "positive" there must be some showing that the actual quantity of the compound in the urine that caused the reaction is a true reading.

The gross screening tests which, alone, would be a basis for finding a sample "invalid" are not sufficiently precise and accurate to justify this conclusion. We submit that canceling any such test result is the more reasonable approach until testing meets appropriate scientific standards.

4. Quality Controls Are A Vital Part Of Any Testing Scheme.

We are pleased to see that the proposed regulations have included and enhanced the quality control requirements enumerated in NLCP Program Document #37, Notice to HHS Certified Laboratories and Inspectors, Subject: Specimen Validity Testing (July 28, 1999) ("PD 37"). Experience has shown the large number of incorrectly reported results, and the significant number of employees adversely affected when such protocol is not followed. It is absolutely vital that such protections be included in any testing scheme, and we are glad to see them included here.

B. The Claim That Urine Reported With Creatinine Of Less Than Or Equal To 5 mg/dL And Specific Gravity Of Less Than Or Equal To 1.001 Cannot Be Considered Human Urine Is Contrary To Actual Experience And Study Results.

There has been no showing by either HHS or DOT that a urine sample with creatinine and specific gravity below the regulated cutoffs cannot be human urine. For this reason, it is essential that any such cutoffs be used, at most, as only a trigger for the need to obtain additional information, and not as a presumption of individual wrongdoing with the burden placed on the employee to prove his or her "innocence." As recent experience (limited as it has been) has shown, there are several factors that may contribute to a sample being reported as below the cutoffs.

1. It Is Necessary To Account For Laboratory And Other Errors.

It is important to recognize that the levels reported may not accurately reflect the actual levels of creatinine and the specific gravity of the urine. As was shown in the high profile Delta pilot case handled by ALPA, reported levels can be unreliable and inaccurate due to laboratory error. The structure of the DOT rules and the HHS proposed guidelines fails to provide sufficient mechanisms by which a reported result can be overcome where, as there, the reported result is from faulty laboratory work as opposed to "a legitimate medical explanation."

We have previously addressed (and incorporate by reference) the need for employees and their unions to have ready access to information necessary to uncover such laboratory error, both to demonstrate employee innocence and to protect the integrity of the system. (See attachment 3, incorporated by reference).[5] However, it should also be recognized that it is extremely time consuming and exorbitantly expensive to investigate and uncover such laboratory error. The magnitude of that undertaking will likely deter innocent individuals (especially non-represented workers), or result in futile attempts that are unsuccessful due to lack of resources and specialized expertise. That burden should not fall on individual employees, or even their labor unions.

[5] Union access to such information should include laboratory oversight and quality assurance documents, such as laboratory proficiency checks, inspection reports and critiques, etc. See e.g., material referenced in Section 3.2(b). 66 Fed. Reg. at 43882. Allowing unions and other interested parties to serve as "watch dogs" is a useful function that fosters the integrity of the program. ALPA's identification of the problems at LabOne that led to a special HHS investigation causing the cancellation of 300 test results, illustrates this point.

2. Humans Do Produce Urine With Creatinine And Specific Gravity Below The Proposed Regulatory Cutoffs.

Another reason for a so-called "substituted" result may be that the individual is one of the small minority of those whose body produces ultra-dilute urine. While we agree that the overwhelming majority of individuals will not have urine with measures at these levels, a small percentage of otherwise healthy people (due to their physiology, diet or other factors) will produce readings at or close to the proposed cut offs. And in a program of this magnitude covering millions of workers,[6] even a fraction of a percentage of the covered employees yields a significant number of individuals at risk of losing their careers.

Contrary to the government's claims that specimens below the proposed cutoffs must be treated as non-human urine, experience has shown that individuals producing such urine exist, and have come forward with such samples obtained under direct observation. We have also seen that an individual may have a sample above the cutoffs on one occasion, and then produce urine below the cutoffs (again, under direct observation) on another.

Such cases have likewise been confirmed by the MROs.

> [t]here have been a few cases where MROs have personally observed the production of specimens that have subsequently been reported as substituted. Thus, it does appear that the proposition that it is impossible to physiologically produce substituted urine is not a sustainable one.

Theodore F. Shults, MS, JD, The MRO's Oversight of the Referral Physician, MRO ALERT at 4, Vol. XII, No. 3 (April 2001) ("MRO ALERT").

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[6] DOT says that its testing program covers 8.34 million employees. 64 Fed. Reg. at 69,093. Millions of federal employees are subject to compulsory testing as well.

The literature reviewed by HHS and DOT (66 Fed. Reg. at 43,877), also fails to prove that individuals cannot produce urine with readings below these cutoffs. The extremely limited value of the studies cited in NLCP: State Of The Science: Update #1, Subject: Urine Specimen Validity Testing: Evaluation of the Data Used to Define a Urine Specimen as Substituted (Feb. 14, 2000)("NLCP #1") (attachment 4) was discussed in detail in ALPA's Comments to the Part 40 NPRM. (Attachment 3 at 25-31). In sum, a review of the data revealed the appalling dearth of "paired data" – data from specimens where both the creatinine level and the specific gravity was measured. Notwithstanding the 45 different papers cited,[7] individual paired data was presented from only eight men and two women, described in four papers. Unquestioningly, so few studies with such limited data are scientifically and statistically inadequate to confirm the proposition that urine with creatinine and specific gravity at or below the cutoff cannot be human urine.

Moreover, many of the remaining studies – none of which actually measured specific gravity and creatinine in the same urine sample – do show that particular individuals' urine had one variable that measured at or below the "substitution" cutoffs. For example, in nine different studies the specific gravity of 20 subjects' urine was at or below the cutoff.[8] Subjects' urine had creatinine at or below the cutoff in other studies.[9]

[7] The bibliography references 48 numbered studies but 3 of them were listed twice.

[8] Specific gravity at 1.000 was reported in 12 subjects and 12 specimens in the following studies: E.J. Cone et al., In Vivo Adulteration: Excess Fluid Ingestion Causes False-Negative Marijuana and Cocaine Urine Test Results, Journal of Analytic Toxicology, 22:460-73 (1998); G.M. Homer et al., A Discussion of Creatinine Analysis in Single Collection Urine Specimens, Journal of Forensic Sciences, 38:501-02, (1993); W.V.R. Vieweg et al., Psychogenic Polydipsia and Water Intoxication – Concepts that Have Failed, Biol. Psychiatry, 20:1308-20 (1985); G. Rinard, Water Intoxication, American Journal of Nursing, 89:1635-38 (1989); R.T. Frizzell et al., Hyponatremia and Ultra-marathon Running, JAMA, No. 6, 265:772-74 (1986). Specific gravity of 1.001 was

The more recent paper cited in the NPRM, The Characterization of Human Urine for Specimen Validity Determination in Workplace Drug Testing: A Review, Journal of Analytical Toxicology 24:579-88 (2000), revealed similarly few relevant scientific studies and no conclusive support for the contention that urine with creatinine and specific gravity below the cutoffs cannot be human urine. As the authors noted, "A review of the literature revealed no studies that specifically posed and answered the question 'How can one determine with certainty whether a specimen is urine or not.'" Id. at 582. Accordingly, that article referenced the same random urine clinical studies, medical overhydration studies, and water loading studies identified in NLCP #1. The only new data it referenced is from some additional medical overhydration studies, none of which included paired data. It should be noted, however, that many of the specimens in those new studies reported specific gravity at or below the regulatory cutoff.[10]

Nor does the limited study of creatinine and specific gravity readings of selected employees, conducted by DOT, prove that an individual cannot produce urine below the cutoffs. To the contrary, the data suggests that individuals – particularly women – will

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reported in 8 subjects and 25 specimens in the following studies: R.A. Braithwaite, An investigation into the extent of possible dilution of specimens received for urinary drugs of abuse screening, Addiction, 90:967-70 (1995); S.L. Nickman et al., Further Experiences with Water Intoxication, Pediatrics, 41:149-51 (1968); and M. Okura, M. and S. Morii, Polydipsia, Polyuria and Water Intoxication Observed in Psychiatric Inpatients, Tokushima Journal Exp. Med., 33:1-5 (1986).

[9]See e.g., S. George and R.A. Braithwaite, An investigation into the extent of possible dilution of specimens received for urinary drugs of abuse screening, Addiction, 90:967-70 (1995); E.J. Cone et al., In Vivo Adulteration: Excess Fluid Ingestion Causes False-Negative Marijuana and Cocaine Urine Test Results, Journal of Analytic Toxicology, 22:460-73 (1998); W.V.R. Vieweg et al., Psychogenic Polydipsia and Water Intoxication-Concepts That Have Failed. Biol. Psychiatry 20:1308-20 (1985).

[10] Id. at 583, Table VI., references 48-71.

produce urine with readings at these levels. That study looked at paired measurements in 54 volunteers, 41 of whom were women. It should be noted, however, that there were serious flaws in the study protocol, which could have skewed the results.

First, cigarette smoking or the use of products or medications containing nicotine was not controlled. Nicotine is well recognized as inhibiting dilution of urine by water loading. As a result, creatinine values on urine dilution from populations that contain smokers will be much higher than such levels in non-smoking populations. See J. Cates and O. Garrod, The effect of nicotine on urinary flow in diabetes insipidus, Clin. Sci. 10:145 (1951); J. Walker, The effect of smoking on water diuresis in man, Q. J. Med. 18:51 (1949); W. Chin et al., Water intoxication caused by smoking in a compulsive water drinker, Clin. Res. 24:625A (1976).

Second, the study included the participants' first urine specimen after awakening, on both the first and second morning of the test collections. First morning urine is far more concentrated than urine randomly collected during the day. See M. Krieg and K. Gunser, Quantitative analysis of clinical and chemical parameters in the 24 hour urine and in the morning. J. Clin. Chem. Clin. Biochem. 24:863 (1986); W. Ottinger, A discussion of creatinine analysis in single collection urine specimens, Journal Forensic Sciences 38:501 (1993); C. Ricos et al., Biological variation in urine samples used for analyte measurements, Clin. Chem. 40:472-77 (1994). Accordingly, including such data in the analysis would skew the results, making the creatinine levels higher than those from urine produced for random drug tests. For example, the study abstract reports that 113 of the 500 specimens, or 22.6%, were "dilute." However, if the 112 first morning urine specimens are subtracted from the data as not representative of random specimens, this would make 113 of 388, or 30%, dilute.

Third, the specimens were not "blinded" to the laboratory, and the study lacked controls. Such controls should have included non-urine specimens, as well as nonhuman urine, to test whether laboratory testing can distinguish between nonhuman and human urine, and non-urine liquids and human urine. Ordinarily such controls would be part of any scientific study subject to peer review. Moreover, neither the agency authorizing the study or the researchers conducting it, were disinterested parties. The researchers included individuals who had previously endorsed the regulatory creatinine and specific gravity cutoffs and had a professional interest in having them validated. Unwittingly, that bias could have affected the data reporting and analysis.

Fourth, the study encompassed a relatively small number of people not statistically significant enough to be representative of the population. Nor is the number of women subjects - 41- a sufficient quantity from which to draw conclusions representative of all females. It is also significant that the study did not track or identify the female subjects' place in their menstrual cycle. Creatinine output in women varies during the menstrual cycle. See M. Gault et al., Mid-menstrual cycle decline in creatinine and urea clearances, Nephron 67:158-66 (1994). Thus, it is not known what impact the failure to track or control for that variable had on the data.

Fifth, the study also failed to include any significant number of low weight and small body mass participants – especially women, who are at the greatest risk for producing low levels of creatinine. Only nine of the 54 participants were women weighing 115 pounds or less. As such, it failed to test any representative number of the type of individuals most likely to have low creatinine levels.[11]

Yet, despite these flaws, **three of the subjects – or nearly six percent of the group – produced specimens at the "substituted" level within the margin of error of the method and the laboratory procedures.**[12] Although, as we have discussed (supra at 5-6) the precision of the test is not actually known, if we conservatively assume the test has a standard deviation of ±.1 mg/dL (a coefficient of variation of 2%),[13] then a specimen with a true value of 5.1 mg/dL would test between 5.0 and 5.2 68% of the time, and between 4.9 and 5.2 mg/dL 95% of the time. N. Tietz, Textbook of Clinical Chemistry 48-51 (Philadelpia, W.B. Saunders Co. 1986). **This means that a person with creatinine at 5.1 mg/dL would likely report a result of 5.0 mg/dL or lower -- 33% of the time.**

If, however, the precision is actually less, a greater number of specimens will read lower than their actual levels a greater percentage of the time. So, for example, if the

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[11] It is noteworthy that the study showed that even women with sizable body mass could consistently produce dilute urine. For example, subject "S1" – a 26 year old women weighing 165 pounds and 67 inches tall, consistently produced dilute specimens.

[12] Subject "E17" (an Asian female) produced urine with 5.2 mg/dL of creatinine and 1.002 specific gravity after drinking 1004 ml in three hours. Subject "E20" (a white, female) produced five dilute specimens, the lowest of which were 5.1 mg/dL of creatinine and 1.001 specific gravity; and 5.6 mg/dL of creatinine and 1.001 specific gravity, apparently, after drinking 5202 ml of water over eight hours. Subject "S1" (a white, female) produced eight dilute specimens, the lowest of which were 5.2 mg/dL and 1.001, and 5.8 mg/dL creatinine and 1.001 specific gravity, apparently, after drinking 2740 ml over five hours.

[13] This coefficient of variation is based on data provided by the manufacturer of the Olympus Creatinine Reagent when it is used to measure creatinine in blood. (Attachment 5). Of course, there has been no showing that the same precision applies when the test is used to measure urine.

standard deviation is ±.25 (a coefficient of variation of 5%), then a specimen with a true value of 5.1 would test between 4.8 and 5.3 mg/dL 68% of the time, and between 4.6 and 5.6 mg/dL 95% of the time. **This means that a person with creatinine at that level - like the woman in the study – would likely report a result of less than 5.0 mg/dL - 50% of the time.**

At this juncture, however, the amount of error that is tolerated in these tests is unknown. Whether the coefficient of variation or the "precision" of a particular assay or screening test is 1%, 2%, 5% or even more, will determine the range of values within which a known quantity is expected to measure.

There is also the question of how much variation is allowed at a laboratory <u>between</u> the different runs on known controls. This too must be taken into account in assessing whether a reported result is truly within the "normal" range for creatinine levels.

These findings do mean, however, that if a larger group of subjects had been used, it is likely that additional data at or below these levels would have been obtained. Accordingly, contrary to the conclusion reached by DOT and HHS, the study suggests that individuals can produce urine with creatinine and specific gravity levels measuring at or below the cutoffs.

Others reviewing the study have reached the same conclusion. Noting the relatively low "*n*-" numbers, Theodore F. Shults of the American Association of Medical Review Officers, observed

> The limited data that has been compiled shows (or at least statistically suggests) that it is not physiologically impossible to produce substituted urine. What is revealing about the study is that one volunteer had urine that was right on the border of being identified as a substituted specimen.

> This borderline data point is significant. Although it is not "technically" substituted urine, one should ask what is the "technical" standard deviation measurement of creatinine here? It is certainly not zero; thus the measurement could easily have been below the 5.0 cutoff level for creatinine. So at best there is a zero margin of safety. Statistics would also indicate that in a similar study with larger *n*- numbers and a normal distribution of data, some incidence of data points would be identified as meeting and exceeding the substituted criteria.

MRO ALERT at 4.

The results of the DOT study also contradict the "theoretical dilution limits" of urine as identified in the literature review cited by HHS. See The Characterization of Human Urine for Specimen Validity Determination in Workplace Drug Testing: A Review, Table IV, Journal of Analytical Toxicology 24:579-88 (2000). The scientific paper stated that with a daily urine output of one liter (identified in the text as the "normal" excretion volume), the lowest possible value of creatinine is 50 mg/dL, and the lowest possible specific gravity is 1.019. The article indicates that with a level of fluid consumption of 10 liters or more per day, the lowest possible value of creatinine is 5.0 mg/dL and the lowest specific gravity is 1.002. Id.

In DOT's limited study with its inherent flaws, the subjects produced much lower levels of creatinine and specific gravity, based on much less fluid consumption, and over a shorter period of time than the theoretical limits. Three subjects and five or more specimens reached the theoretical limits of 5 mg/dL and 1.001 specific gravity (even assuming the precision of the tests is 2%) after drinking only one to five liters of water over three to eight hours.[14]

This data and our actual experience shows that the "absolute" limits of creatinine and specific gravity levels in human urine differ from the theoretical concepts. It also

[14] Supra at 19, n.12.

shows that otherwise healthy individuals – without any serious or unusual medical conditions, and without having tampered with their specimens – can and do produce urine below the creatinine and specific gravity cutoffs. Such data must be seriously considered and the limits eliminated as proposed.

C. Additional Procedural Protections Should Be Added To Support The Integrity Of Any Validity Tests.

It is not acceptable to leave the degree of error in a testing device to the test manufacturer, or to allow laboratories to establish the margin of error for their procedures as they deem fit. Any such mandated testing, with mandatory employee sanctions, should ensure that the applicable testing methods and laboratory methodology comply with strict standards with respect to precision and accuracy.

Once the margin of error of the validity tests is established - including the precision, accuracy, false positive rate, etc. - it is essential that this range be added to the reported values of test results for creatinine and specific gravity, to ensure that employees are not penalized as a result of variable screening results. Thus, if the margin of error of a testing method for creatinine is ± .1, than a 4.9 reading should be recognized as capable of actually being 5.0. This approach has been required of other forensic laboratories in other countries. See International Standard Organization ("ISO") Standard 17025 (1999).

Additionally, the other means by which reported results can be distorted should likewise be recognized in the process. MRO's should be given instruction about testing limitations and the uncertainty of the measurements. Recognition of such test limitations should be taken into account in the regulatory scheme. MROs should also be trained on the physiological (and other) reasons why otherwise healthy individuals may have readings below any regulatory cut-offs.

Finally, we urge that any regulatory standards recognize that innocent people can produce urine with creatinine and specific gravity readings at or near the currently proposed cut-offs. Individuals should not suffer adverse consequences merely for producing ultra-dilute urine by having their samples deemed "substituted" or "invalid." If drug testing on such samples cannot be accomplished within the bounds of scientific certainty, then those tests should be cancelled. The focus should remain on testing for the detection of illegal drugs as opposed to penalizing employees for ultra-dilute urine, or uncorroborated results on non-specific oxidation tests.

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Dated: October 22, 2001

TTD AFFILIATES

The following labor organizations are members of and represented by the TTD:

Air Line Pilots Association
Amalgamated Transit Union
American Federation of State, County and Municipal Employees
American Federation of Teachers
Association of Flight Attendants
American Train Dispatchers Department
Brotherhood of Locomotive Engineers
Brotherhood of Maintenance of Way Employes
Brotherhood of Railroad Signalmen
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International Association of Fire Fighters
International Association of Machinists and Aerospace Workers
International Brotherhood of Boilermakers, Blacksmiths, Forgers and Helpers
International Brotherhood of Electrical Workers
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International Longshoremen's Association
International Longshoremen's and Warehousemen's Union
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Office and Professional Employees International Union
Professional Airways Systems Specialists
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Service Employees International Union
Sheet Metal Workers International Association
Transportation • Communications International Union
Transport Workers Union of America
United Mine Workers of America
United Steelworkers of America

October 2001

Transportation Trades Department, AFL-CIO

BEFORE THE
DEPARTMENT OF TRANSPORTATION

In the Matter of: PROCEDURES FOR TRANSPORTATION WORKPLACE DRUG AND ALCOHOL TESTING PROGRAMS	Docket No. OST-99-6578

COMMENTS OF THE AIR LINE PILOTS ASSOCIATION

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COMMENTS OF THE AIR LINE PILOTS ASSOCIATION

Introduction and Summary

The Air Line Pilots Association ("ALPA") is the principal labor union representing the nation's commercial pilots. It represents more than 55,000 pilots at 51 airlines in the United States and Canada. ALPA submits these comments in response to the above-captioned Notice of Proposed Rulemaking ("NPRM").

ALPA reiterates here its long-standing commitment to the advancement of air safety and its opposition to all forms of drug and alcohol abuse by aviation personnel, especially pilots. As an industry leader in developing and implementing the highly successful Human Intervention Motivation Study (HIMS), ALPA remains convinced that the best way to prevent, identify and eradicate any pilot substance abuse is through a specially tailored peer-intervention, employee assistance and rehabilitation program.

While we recognize that random drug and alcohol testing is required by law, we nonetheless maintain our view that such mandatory testing is a fundamentally misguided approach. In our view, such testing has been exorbitantly expensive with very little return. The data we have seen shows a consistently minuscule number of positive drug test results for currently employed, flight crew members -- a rate of about one tenth of one percent of positive random drug tests. This substantiates our contention that the incidence of substance abuse among commercial pilots is very low, and that random testing is an ineffective means of identifying any such problems. The vast numbers of dollars spent on the current mandatory testing programs would be far better spent on making programs, such as the HIMS program, stronger and more widely available.

Although Congress imposed mandatory drug and alcohol testing, it did so only after mandating significant protections to employees to ensure the highest degree of scientific accuracy of such tests. We are gravely concerned that DOT is now proposing to impose another form of testing, "validity" testing, without requiring several of the same fundamental safeguards.

The testing methodology proposed fails to meet even generally accepted scientific standards, let alone the forensic standards that should apply when adverse test results will end employees' careers. Application of the testing methodology as proposed would present serious risks that innocent employees could be falsely reported as having adulterated (or substituted) their urine samples and lose their jobs as a result. In addition to concerns about the accuracy of the reported "validity" test results, we are also disturbed about the proposal which would implement automatic cutoffs for dilute urine and treat an employee as a rule violator merely because he or she has ultra-dilute urine without any evidence of individual wrongdoing. Reporting employees as having adulterated or substituted their urine samples based on potentially inaccurate testing methodology and automatic cutoffs violates employees' due process rights.

The NPRM also proposes to require directly observed urine testing in a greater number of circumstances, and to eliminate the safeguards that presently ensure that any such testing will be narrowly circumscribed. We strongly object to these provisions of the current proposals which would require employees to be directly observed while urinating into specimen bottles. The proposals are much more intrusive, infringe privacy rights to a much greater degree, and are not justified under the circumstances and in the manner suggested by DOT.

We also object to any changes in the regulations that would require employees to "stand down" from service after a laboratory reports a positive drug result, but before the rules' procedural requirements have been satisfied to verify that the employee has, in fact, engaged in illegal drug use. Such protections were designed to ensure that employees not be falsely identified as illegal drug users, and should continue to protect employees from that risk.

We do support the provisions that would require greater training for Medical Review Officers ("MROs"), Collectors, Testing Technicians, and Substance Abuse Professionals ("SAPs"). Such training and recurrent training is essential. We also support DOT's proposals to ensure greater accountability of third-party service providers and believe that there should be a mechanism for such individuals or entities to be prohibited from providing services if they fail to abide by Part 40 procedures.

In our view, blind specimen testing is an important quality assurance safeguard and should be maintained. DOT should also require the inclusion of blind samples of any compounds or solutions (such as adulterants) that are to be tested in urine as part of any "validity" testing program.

Additionally, we urge DOT to reaffirm the obligation of employers, service agents and laboratories to provide employees and labor unions with relevant information. The broad range of this information should be explicitly described. Finally, we recognize and appreciate DOT's effort to revamp the rule and make its contents more accessible and understandable to readers.

I. REQUIRED "VALIDITY" TESTING

It bears emphasis that ALPA not only opposes illegal drug use, but also opposes employees adulterating or substituting their urine samples. What we are gravely concerned about, however, is the mandatory imposition of screening tests -- the results of which may brand an employee as having adulterated or substituted a urine sample -- when such tests fail to meet appropriate scientific standards and may be grossly inaccurate. We are also greatly disturbed that DOT has relied upon inadequate data to mandate cutoff levels of creatinine and specific gravity, and is seeking to require that employees whose urine is reportedly below those cutoffs be automatically treated as if they had substituted their samples.

When drug testing of safety-sensitive transportation employees was first proposed there was tremendous concern about assuring the scientific accuracy of the testing process, implementing safeguards against false positives, and assuring that an employee not be charged with illegal drug use where there was a legitimate medical explanation for the test result. It was well recognized that a verified, positive test for the presence of illegal drugs would often end that person's career, and protections were implemented to avoid employees being wrongly or falsely charged.

A report of "adulteration" or "substitution" for an employee, is as, or even more, serious than a positive result for illegal drugs. Unquestionably, such charges, like a positive drug test, will often result in the termination of the employee. Pilots charged with "adulterating" or "substituting" their urine samples are treated as having "refused to submit" and additionally face revocation (often emergency revocation) of their pilots' certificates by the FAA. Yet, despite the grave ramifications of an adverse "validity" test result, the proposed regulations lack the important safeguards required by law and regulation that are present when urine is tested for the presence of illegal drugs. Nor do the proposed regulations recognize that it is possible for a small percentage of employees, especially extremely hydrated flight crewmembers, to have ultra-dilute urine on occasion without engaging in any wrongdoing.

Our recommendations for the protections and limitations that should be incorporated in any program of "validity testing" are as follows. Our suggestions are based in part on the observations and critique provided by well-respected Forensic Toxicologist, Dr. Vina Spiehler. Attachment 1 to our Comments is a report by Dr. Spiehler ("Spiehler Rep.") to which we refer, as well as her Curriculum Vitae, and two recent articles by Dr. Spiehler (Attachment 2).

A. THE ACCURACY OF THE REPORTED RESULT MUST BE ASSURED.

1. The Necessity Of A Second Test Confirming The Measurement Of The Compound (Or Property) Based On A Different Chemical Or Physical Property Of The Analyte.

Under the proposed regulations, a laboratory is required to use only one testing methodology when testing for adulterants or creatinine or when measuring specific gravity. This contravenes the fundamental principle in forensic toxicology, that in order to assure an accurate test result, at least two different analytical techniques must be used. See Spiehler Rep. at 2, citing American Academy of Forensic Sciences Policies on Confirmation; Reese, J.J., A Manual of Toxicology (1874); Levine, B., Principles of Forensic Toxicology (1999); American Academy of Forensic Science/Society of Forensic Toxicologists Forensic Toxicology Laboratory Guidelines. As Dr. Spiehler explains, the scientific basis for this principle is that "the consistent, corroborative findings of independent tests of the same value or fact increases the probability that the finding is true." Spiehler Rep. at 2. A second, truly independent test must utilize a procedure based on a different chemical or physical property of the analyte. Id. at 3. The failure of the proposed standards to require a confirmation test utilizing a different testing methodology is a serious flaw in the procedures which can cause grossly inaccurate test results.

Under the proposed regulations, an employee's single, uncorroborated screening test would be the sole basis for determining whether that employee is guilty or innocent of violating the drug testing rules. Such screening tests alone may have a predictive probability of no greater than 75%. Spiehler Rep. at 4. Of course this means that a full quarter of all such tests may be false positives, and that substantial numbers of employees could be falsely charged with adulterating (or substituting) their samples based on these tests. Such risks should be wholly unacceptable.

Both Congress and DOT rejected the approach of using a single, screening test as the sole basis for determining whether an employee had consumed illegal drugs. The Omnibus Employee Testing Act requires that scientific and technical guidelines be utilized that establish comprehensive standards for laboratories, "including standards requiring the use of the best available technology to ensure the complete reliability and accuracy of controlled substances tests . . . ." 49 U.S.C. § 45104(2)(A) (emphasis added). The Act also requires that any laboratory involved in such controlled substances testing "have the capability and facility, at the laboratory, of performing screening and confirmation tests;" and that all tests indicating the use of controlled substances "be confirmed by a scientifically recognized method of testing capable of providing quantitative information about . . . a controlled substance." Id. §§ 45104(3) and (4) (emphasis added).

DOT's urinalysis drug testing procedures include the required confirmation test and utilize "the best available technology," the GC/MS test, for such confirmation. An explanation of the value of using such confirmation testing was offered by the FAA in responding to concerns about the risks of drug testing inaccuracies when it promulgated its drug testing regulations in 1988.

The FAA recognized that when drug testing was introduced in the military and elsewhere in the early 1980s, false positive test results occurred but were found primarily in analysis of specimens during the initial screening process. 53 Fed. Reg. 47032 (1988). While noting that the immunoassay screening tests had since become more sophisticated, the FAA sought to allay concerns about false positives by requiring independent, confirmation testing by the highly accurate GC/MS test.

> Despite its increased accuracy, the initial screening test remains a less expensive test used only to yield a preliminary indication of the possible presence of drugs or drug metabolites. In order to ensure the integrity and accuracy of any test result, each positive initial screening test result must be confirmed using GC/MS analysis or another confirmatory procedure that may be subsequently approved by DHHS and incorporated into the DOT procedures. The GC/MS confirmation test is an extremely accurate and sophisticated test and is virtually error-free when used in compliance with the DHHS guidelines.

Id.

The standards that must be satisfied before a laboratory can report a verified drug positive, are in accordance with those recognized by the scientific community. An initial screening test must then be independently substantiated by a confirmation test using different physical or chemical properties of the drugs. Requiring an immunoassay test to be confirmed by the GC/MS methodology results in a highly accurate procedure. Dr. Spiehler states that the probability that the result is correct is at least 99.9%. Spiehler Rep. at 3-4. The

FAA cited accuracy claims of "virtually 100 percent . . . , assuming that proper chain-of-custody procedures are followed." 53 Fed. Reg. 47032 (1988). Unquestionably, any required "validity" tests should be held to the same standards of scientific accuracy. Mandating other urinalysis testing that will likewise be career-determinative but whose accuracy is less stringent is contrary to the intent of the law, and would deprive employees of due process.

Yet this is exactly what DOT's proposed procedures would do. Instead of requiring an initial test for adulterants followed by an independent confirmation test, the NPRM merely requires that the same test be repeated on two different aliquots. As Dr. Spiehler notes, repeating the same test twice does not add to the degree of accuracy of the test result. "Repeating the test or using a dip-stick version of the same reaction as a 'confirmation' would not increase the probability that a positive result is a true positive because the second test is not independent and would be subject to the same errors and interferences as the first." Spiehler Rep. at 4.

The proposed testing protocol to measure urine dilution suffers from the same deficiencies. "Combining screening tests for specific gravity with screening tests for creatinine is not appropriate confirmation of dilution, substitution or adulteration as there would be no accurate confirmation of the initial analyte value and the literature suggests that the two are not independent tests of urine dilution." Id.

Screening tests and confirmation tests utilizing different testing methodologies are readily available to test for adulterants and measure urine dilution. Dr. Spiehler discusses some of the particular screening tests and confirmation tests in her Report at 5. She notes that the tests currently being used by laboratories under DOT guidelines in testing for creatinine, specific gravity, gluteraldehyde, nitrites and pH are non-specific colorimetric tests which are suitable for screening. The methodology for confirmation testing of analytes such as creatinine, gluteraldehyde or nitrites should be chromatographic. Such tests are commonly performed by laboratories and readily available. See id. Confirmation methods for aqueous solutions such as pH, specific gravity and osmolality should be direct measurements of the definition property, not estimates from a related or associated property.[1] Id.

It is essential that any new, mandated testing for urine to confirm its "validity" have the same high degree of accuracy and meet the same legal and scientific standards that exist for drug testing. Any "validity" test should be

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[1] We believe DOT's attempt to identify employees who substitute their samples by the degree of dilution of their urine is a misguided and seriously flawed approach. See discussion at 20-31, infra; see also Spiehler Rep. at 8-9 (questioning the appropriateness of using specific gravity as indicator of dilute urine). However, it should also be noted that procedures proposed for taking that measurement are inappropriate. Currently, the sole method being used to "measure" specific gravity is not even a direct measure of the property. Rather laboratories are using screening tests that indirectly estimate a level of specific gravity. But before any laboratory certifies an employee's level of specific gravity – particularly if that reading can have severe employment consequences – it must be confirmed by a method that, in fact, directly measures specific gravity. This is done by a hydrometer or a balance.

confirmed by a second testing methodology before it is reported by a laboratory as a "certified" result.[2]

2. The Safeguard Of Analysis Of The Split Sample By A Second, Certified Laboratory Should Be Required For Any Adulterant (Or Other "Validity") Testing.

Analysis of a split sample by an independent laboratory has always been regarded as an extremely important safeguard for employees. The drug testing program initially implemented by the FAA permitted (but did not require) split sample analysis, which employees did not consider sufficiently protective. This concern became a major issue before Congress when it was considering mandatory drug testing legislation for aviation (and other transportation) employees. Congress ultimately recognized the significance of this protection to employees and to the overall integrity of the testing program and legislated the right to this safeguard. See 49 U.S.C. § 45104(5).

Inherent in the need for this protection is the recognition that laboratories do make mistakes, and tampering with a specimen can occur. The right to have a split sample of the employee's original urine analyzed by a second, certified laboratory -- using different equipment and different personnel -- assures that an employee is not reported as having used illegal drugs based on laboratory error or misconduct. It provides a key piece of evidence that can save innocent employees' careers and prevent unlawful deprivations of property.

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[2] MRO review must also be required before the report of a "validity" test result can be "verified" as positive. See discussions pp. 17-19, infra.

The need for this safeguard is just as great, if not greater, for urinalysis testing for adulterants (or other "validity" tests) that pose the same career-ending consequences if inaccurate. The risks of laboratory error or misconduct are identical for any type of laboratory urinalysis testing. There certainly is no less risk of harm where urine is being analyzed for the presence of adulterants instead of drugs.

There may be an even greater risk of certain compounds commonly found in adulterants getting into a specimen bottle through laboratory error, or sloppy procedures. Gluteraldehyde -- one of the "adulterants" for which DOT proposes to test -- is a component of disinfecting solutions commonly used in laboratories, and is contained in some cleaning agents that may well be present, at or near the collection site.

DOT's proposal to analyze other aliquots from the original sample at the same laboratory does not provide the necessary protection and will not cure the problem if it was that laboratory's procedures which, in fact, contaminated the sample.

Nor has DOT presented any good reason why split sample analysis cannot apply in the same manner to adulterant and other "validity" testing, as it does in the realm of drug testing. The concern expressed -- that adulterants may deteriorate over time and may no longer be present at the time of the split analysis -- is no different than the issue faced (and addressed) in marijuana detection. Because the marijuana metabolite is not stable over time, a lower quantitative threshold is used for the confirmation test than on the screening test, and an even lower threshold is used for the analysis of the split. The threshold for the screening test is 50 ng/ml, 15 ng/ml on the confirmation test. 49 C.F.R. § 40.29(e)(1) and (f)(1). Confirmation of the drug on the split sample is conducted "without regard to cutoff levels." 49 C.F.R. § 40.29(b)(3). This same approach could be used for split analysis of adulterants, or other "validity" tests.

Another equally viable approach would be to provide for the immediate, automatic analysis of the split sample by a second, certified laboratory in cases where a verified positive is reported for an "unstable" compound.

The split sample protection can and should be implemented for any urinalysis testing. The intent of Congress in ensuring that an employee not be wrongfully treated as an illegal drug user if his verified positive test is not confirmed by a second, independent laboratory, applies equally to "validity" tests. Congress did not consider adulterant or "dilute" urine testing when it passed the Testing Act, and we have found no evidence in the legislative history that any such testing was contemplated. In our view, analyzing compulsorily provided urine pursuant to the Testing Act, but without providing protections in accordance with the Act is contrary to the language and intent of the law.

3. Any Screening Tests Used To Detect Adulterants Or Measure Urine Dilution Must Be Subject To The Same FDA Review As Required For Drug Screening Immunoassay Tests.

The regulations currently require that the immunoassay tests used for screening for drug or drug metabolites must be cleared or approved by the Food and Drug Administration ("FDA"). 49 C.F.R. § 40.29(e). Such review identifies the diagnostic sensitivity (true positive rate), diagnostic specificity (true negative rate), and predictive value for detection of the compound (or property) being tested.

While the screening tests currently being used for "validity" testing (and which would be permissible for that use under the proposed rules) have been cleared or approved for other purposes – such as to identify bacterial infections, or to test renal function -- they have not been assessed for their ability to identify adulterants, or to validate urine (and to do so at the cutoff levels proposed). See Spiehler Rep. at 5. Review of the predictive probabilities of the tests in this regard is essential. It is vital to identify these parameters since they determine the error rate of the test being used. The accuracy of the screening test, together with the accuracy of the confirmation test, determine the accuracy of the final "verified" reported test result.

Identification of the error rate of a scientific test that may be the basis for ending a person's career is essential. Clearly, the error rate is a relevant factor in determining whether a scientific test is valid and reliable. For this reason, the Supreme Court has recognized that when evaluating the admissibility of evidence involving a particular scientific technique, the known or potential rate of error must be considered. Daubert v. Merrell Dow Pharmaceuticals, Inc., 509 U.S. 579, 594 (1993). Just as this information was found to be essential for drug screening testing methodology, so too should it be required for adulterant or other "validity" screening tests.

4. The NPRM Fails To (And Should) Incorporate The Minimal Safeguards In SAMHSA PD 37.

Although "validity" testing has been voluntary thus far, DOT, HHS and SAMHSA have issued guidance setting forth required standards and procedures to govern any such testing. In July 1999, SAMHSA issued NLCP Program Document 037[3] ("PD 37"), in part, in response to objections from scientists and NLCP inspectors about the way in which such voluntary testing was being implemented. Spiehler Rep. at 6.

While we have highlighted above some of the most important protections that must be incorporated in any "validity" testing program and do not endorse everything in PD 37, there are some important safeguards that PD 37 implements which we believe should also be included in any such program.[4]

Specifically, we seek the inclusion of the requirements for test method quality and independence. These include the requirements that all specimen

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[3] Notice to the National Laboratory Certification Program (NLCP) Inspectors and HHS Certified Laboratories, General Guidance/Criteria for Specimen Validity Testing, Program Document (PD) 37 issued on July 28, 1999.

[4] Apparently some confusion has arisen regarding the interpretation of some of PD 37's provisions, particularly with respect to whether its reference to analysis on two different aliquots requires analyses utilizing two different chemical or physical properties of the analyte. See Spiehler Rep. at 6. As indicated in our preceding discussion, we believe the requirement for analyses using two different chemical or physical properties is essential and should be explicitly stated in the applicable regulations.

"validity" testing methods be validated by the laboratory, be described in the laboratory's Standard Operating Procedure ("SOP"), and be performed with some "open" quality control specimens. The requirement should be maintained that at least one control with actual urine be utilized in the acceptable range, and at least one control with actual urine be utilized in each of the unacceptable ranges, and that each "open" control must be analyzed with each batch of true specimens being tested.

Additionally, the requirement that results using ≤ (less than or equal to) criteria must be determined to one decimal place greater than the cutoff, should be maintained if such cutoffs are implemented. Truncating a quantitative value is not acceptable with a ≤ decision point of cutoff. As PD 37 notes, "In '≤' scenarios, truncating a quantitative value would change the result from acceptable to unacceptable (e.g. truncating a pH reading of 3.2 to 3 or a creatinine of 5.4 mg/dl to 5 mg/dl)." Should any such cutoffs be implemented in the regulations, the tests that are used to measure the properties in question must be capable of discriminating this level of the analyte. They must be able to accurately differentiate between a pH level of 3.2 versus 3.0 on a confirmation test. Spiehler Rep. at 6. Testing methodology incapable of discriminating between such levels should not be permitted.[5]

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[5] In our view, the foregoing demonstrates that "validity" test results attained under the proposed procedures have the potential to be grossly inaccurate. DOT also proposes to required that any split sample failing to confirm the presence of controlled substances be subject to "validity" testing. Notice of Proposed Rulemaking, OST-99-6578, 64 Fed. Reg. 69076 (proposed Dec. 9, 1999) ("NPRM")

B. MRO REVIEW OF "VALIDITY" TEST RESULTS IS JUST AS, IF NOT MORE, IMPORTANT THAN SUCH REVIEW OVER "VERIFIED" POSITIVE DRUG TESTS; IT IS ALSO ESSENTIAL THAT MRO REVIEW ALLOW THE CONSIDERATION OF INDEPENDENT EVIDENCE.

The importance of MRO review to assure that a "validity" test result reported by a laboratory supports a finding that the employee violated the regulations is just as important as such review of laboratory certified positive drug results. Under the current regulations, MRO review with respect to confirmed positive drug tests "shall include review of the chain of custody to ensure that it is complete and sufficient on its face." 49 C.F.R. § 40.33(a)(1). The assurance that proper chain of custody has been followed is no less important for certified "validity" results and should certainly be included in any such testing program.

We also believe that MROs should be allowed to review other relevant, independent information. The goal of such review should be to confirm that proper procedures were followed and that the result reported is completely accurate. It is absolutely vital that an MRO be able to consider <u>all</u> evidence that may indicate any errors in the chain of custody or elsewhere that may require cancellation of the test. This is particularly so where the employee has evidence

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at 69115 § 40.177. Without completely accurate "validity" test results, this proposal could potentially eviscerate the split sample safeguard as well.

of a procedural error that interfered with chain of custody or could otherwise have affected the integrity of the reported test result.[6]

The NPRM would limit MRO review to solely what appears on the Custody and Control Form ("CCF"). This is an inappropriate constraint that prevents consideration of potentially significant procedural violations that should be considered. While the NPRM identifies "fatal flaws" that require cancellation of tests, there are other errors that can -- and do -- occur, although quite rarely, but which an MRO must be allowed to consider so employees do not unfairly lose their jobs.

At times, collectors have given employees unsealed cups in which to provide their samples, or have allowed employees to leave the testing site without sealing the specimen bottles in their presence. Employees generally trust the collector and the process and, even relatively sophisticated, longtime employees, often lack knowledge of the specific procedural requirements that are supposed to be followed. In such situations, employees are often not aware at the time of collection that the regulatory procedures were violated and, of course,

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[6] Notwithstanding what the final rule states with respect to MRO consideration of independent evidence, it should be made perfectly clear that employers have the right to consider relevant exonerating evidence in making decisions about what discipline, if any, to impose on employees. We think the language of the NPRM may be misleading in this regard, and give the misimpression that constraints on employers regarding actions they must take and information they may (or may not) consider <u>under the rule</u> apply with respect to internal decisions about company discipline. <u>See</u> NPRM, 64 Fed. Reg. 69099 § 40.15(e). The rule should be clarified in this regard.

the collector who failed to follow the correct procedure does not document the error on the CCF.

Moreover, there may be a much greater risk of harm to individual employees from occasional or sporadic lapses in procedure by individual collectors than from the gross errors DOT has seen from certain service providers because systemic problems can be far easier to detect, and are more likely to be considered. The employee tested by a collector who is distracted or performing badly on one particular day may be without any forum to hear of such individual errors.

Concerns about the risks of such error may be even greater with respect to "validity" testing where, if proper procedures are not followed, there may be a greater risk of items commonly found at the testing site (such as soap, disinfectant, or other cleansers) getting into a specimen bottle. In any such case, if the original sample is tainted the split sample will be as well, and the employee will have no other protection.

Finally, just as MROs are required to review evidence of an alternative medical explanation before verifying a drug test as positive, so too should such review be required before a "validity" test result is verified. This could be especially important if any testing for urine dilution is imposed (which we firmly oppose, as described more fully at pp. 20-31, infra), and adverse consequences to employees result from reports of dilute or ultra-dilute urine.

C. DOT'S PROPOSAL TO BRAND EMPLOYEES AS RULE VIOLATORS SOLELY BECAUSE THEIR URINE IS DILUTE IS WHOLLY UNFOUNDED AND UNSUPPORTED BY THE SCIENTIFIC STUDIES.

We recognize that DOT has a legitimate concern in identifying employees who use illegal drugs or tamper with their urine samples to prevent detection of such illegal drug use. We do not condone such behavior. We do not believe, however, that employees should be assumed to be engaging in illegal conduct. Moreover, given the minuscule amount of substance abuse involving pilots, there is even less reason to believe that any notable number of individuals would have any reason to attempt to defeat such testing. Nor is there any evidence of widespread drug testing obstruction among current these employees.[7] And more pertinent to the issue of testing for dilute urine, we have seen no evidence of any substantial incidence of urine substitution among current employees. It appears that in an overzealous attempt to ferret out any employee who might possibly have tampered with a sample, DOT has latched onto the idea of measuring urine dilution and punishing employees with dilute urine. This approach turns on its head the underlying intent of the regulations -- to identify illegal drug users, not employees who consume a lot of water and have dilute urine.

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[7] Of course any problems with pre-employment testing of applicants must be distinguished from those of current safety-sensitive employees.

1. <u>The Procedures Under The Current Regulations Are More Than Sufficient To Identify The Few Employees Who Might Attempt To Substitute Their Urine</u>.

We agree that it is appropriate to identify an employee shown to have substituted a sample and deal appropriately with that person. But the tools for doing so, and the best evidence of substitution, are already contained in the current regulations. As Dr. Spiehler notes, the most likely indicator of substituted urine is urine temperature outside the appropriate temperature range and at variance with the body temperature. See Spiehler Rep. at 10. In this regard, the current regulations provide procedures designed to identify any such urine substitution, along with appropriate employee safeguards. See 49 C.F.R. § 40.25(e).

The current regulations require body temperature to be taken when the temperature of a urine sample is outside the normal range.[8] Where the employee's urine temperature is at variance with the body temperature, or the employee refuses to give a (non-rectal) temperature reading, a same-sex collector, with the concurrence of a supervisor or employer representative, may immediately take a directly-observed urine test. 49 C.F.R. § 40.25(e)(3). Analysis

[8] The NPRM deletes the requirement to take the employee's body temperature, and would immediately require the employee to take a directly observed urine test. We object to this change; comparison of the urine temperature to the body temperature is an important and appropriate check. Various factors might cause a urine temperature to be out of range. For example, if an employee has a fever, both the urine temperature and the body temperature may be unusually high. Looking at the differential between the body temperature and the urine temperature, as required by the current regulations, should be maintained.

(for illegal drugs) of a urine sample procured under direct observation may also provide the best evidence exonerating an employee suspected of tampering.

These provisions provide sufficient and ample means of detecting any employee attempts at specimen substitution. DOT has not made any showing, or presented any evidence, that these procedures are inadequate. There is simply no basis to impose a requirement for estimating urine dilution and labeling employees as rule violators merely because their urine may be ultra-dilute.

2. <u>The Proposed Means Of "Determining" Creatinine And Specific Gravity Are Not Appropriate Or Accurate Measures Of Urine Dilution; Nor Is Specific Gravity A "Confirmation" Of Urine Dilution</u>.

First, by way of background, it is important to note that the muscles in the human body spontaneously produce creatine, of which creatinine is an excretory product found in urine. The quantity of creatine produced (and correspondingly the amount of creatinine excreted in one's urine) varies from person to person, and can vary by as much as 69.9% for a single person, at different times as measured on spot urine tests. <u>See</u> Spiehler Rep. at 7 (citing references). Factors such as amount of muscle mass, the quantity of protein in one's diet, water consumption, gender, and the phase in a woman's menstrual cycle all affect the amount of creatinine produced.[9]

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[9] Measuring the creatinine produced/excreted over a 24 hour period -- "creatinine clearance" -- is a commonly accepted, medical test for renal function. And it is for this purpose, and not as a marker of urine validation, for which the proposed tests have generally been reviewed and approved. (<u>See</u> p. 14, <u>supra</u>.) The NPRM does not propose to use this technique, but rather would merely require a single "spot urine" test.

Thus, while there may be a "normal" creatinine range within which the vast majority of people fall, small numbers of individuals with certain characteristics, particularly those who consume a lot of water, can and do fall below the expected levels. Women, on average, have lower levels of creatinine, and when they eat primarily vegetarian diets, consume great quantities of water, and are at a particular point in their menstrual cycle, may be at greater risk of having ultra-dilute urine, and being deemed to have "substituted" their samples. While DOT proposes to use creatinine levels as an indication of urine dilution in order to identify non-human, or "substituted" urine, as we show below, the urine of extremely hydrated individuals can (and does) fall below these levels.

Under the NPRM, a laboratory is required to "determine" the specific gravity of a specimen if the creatinine in it is found to be < 20 mg/dL. See NPRM, 64 Fed. Reg. 69106 § 40.91(a)(1). (Specific gravity is the relative density of a liquid (or solid) compared to water.) DOT is apparently treating the specific gravity level as a confirmation of a low creatinine level. This approach is seriously flawed in several respects.

First, the literature suggests a variable correlation between specific gravity and creatinine in individuals of from 0.618 to 0.935. Spiehler Rep. at 9 (citing references). This means that sometimes the specific gravity and creatinine correlate, or change in unison, and sometimes they do not. This further means that specific gravity is neither a reliable confirmation of the creatinine level nor a suitably independent measure of urine diluteness to be an accurate basis upon which to determine that an employee substituted his urine. See id.

Moreover, the proposed regulations do not even require an actual measurement of specific gravity. What the regulations contemplate (and what is presently being done under the current "guidance") is an estimate of specific gravity by indirect screening methods such as colorimetry, refractometry or conversion of osmolality measurements. Spiehler Rep. at 9. Use of an estimate of specific gravity introduces yet another margin of error in the level being reported. Such error is highly significant when looking at levels in extremely low ranges and can make the difference between an "acceptable" reading and one which, under the NPRM, would result in the loss of one's career. Although specific gravity can be measured directly, by the use of a hydrometer (urinometer) or a balance, each of which has been calibrated for urine and corrected for temperature deviation from the calibration temperature, laboratories are not required to do so under the NPRM.

Osmolality refers to the total dissolved solids in a liquid, and is usually measured by looking at the change of the freezing point of the liquid being tested. Osmolality is a better measure of dilution than specific gravity because it measures a more detailed property of the liquid. Although the vast majority of the studies relied upon to establish the proposed standards actually measured the osmolality of the subjects' urine, the NPRM does not propose to utilize this more accurate indicator of urine dilution. Spiehler Rep. at 9.

If creatinine and specific gravity are to be measured and used as indicators of urine dilution they must be utilized consistent with appropriate standards of accuracy. Both the level of creatinine and that of specific gravity should each be measured using a screening test, confirmed by a test using a different methodology or property, and then followed by an independent measure of urine dilution such as potassium, urea, or sodium. A third independent measure of urine dilution is necessary because there is not a consistent correlation between creatinine and specific gravity. Spiehler Rep. at 9.

3. DOT's Claim That Urine With Creatinine Of Less Than Or Equal To 5 mg/dL And Specific Gravity Of Less Than Or Equal To 1.001 Must Be Considered As Not Human Urine Is Not Supported By The Scientific Studies.

DOT has repeatedly emphasized that urine whose creatinine level is at or below 5 mg/dL and, at the same time, has specific gravity of less than or equal to 1.001 (or greater than or equal to 1.020) cannot be human urine. As the basis for this threshold, DOT relies on a paper in which Robert L. Stephenson, II, Acting Director of SAMHSA 's Division of Workplace Programs, Center for Substance Abuse Prevention, reviewed and discussed 45 papers.[10] Although it is the

[10] NLCP: STATE OF THE SCIENCE – UPDATE #1, Subject: Urine Specimen Validity Testing: Evaluation of the Data Used to Define a Urine Specimen as Substituted (Stephenson, R.) (Feb. 14, 2000) ("NLCP #1"). The papers referenced -- which include both studies and individual case reports -- are characterized as "Random Urine Clinical Studies," "Medical Overhydration Studies," and "Water Loading Studies." Citations to these studies are by the letter and number designations found in the bibliography in NLCP #1. Although the bibliography references 48 numbered studies, 3 of them are listed twice. The study referenced at A1 is the same as B3, A3 is the same as B6, and A10 is the same as B4.

readings of the two properties together that DOT uses to support its proposed cutoffs, and although Stephenson's paper highlights the "paired data" -- data from specimens where both the urine creatinine and urine specific gravity were measured -- in fact such paired data is shockingly absent.

We agree that "paired data" is the relevant point of reference. But what paired data does DOT rely upon? The proposed standards are based on a total of four papers, involving only 18 subjects, of which only 3 were female, and with data presented from only two of the females.[11] The four papers, however, do not even present individual specimen data for all 18 subjects -- such data from only eight men and two woman is included. See footnote 11. Moreover, two of the studies were done at the same laboratory and involved 16 of the 18 subjects, along with one of the females for whom data is presented.[12]

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[11] The studies are: Goldberger, B.A., Loewenthal, B., Darwin, W.D., and Cone, E.J., Intrasubject Variation of Creatinine and Specific Gravity Measurements in Consecutive Urine Specimens of Heroin Users, Clinical Chemistry, Vol. 41, No. 1, 1995, pp. 116-117 ("A5") (9 male subjects without data for any of them); Coleman, D.E., and Baselt, R.C., Efficacy of Two Commercial Products for Altering Urine Drug Test Results, Clinical Toxicology, Vol. 35, No. 6, 1997, pp. 637-642 ("B2")(1 male subject); Cone, E.J., Lange, R., and Darwin, W.D., In Vivo Adulteration: Excess Fluid Ingestion Causes False-Negative Marijuana and Cocaine Urine Test Results, Journal of Analytical Toxicology, Vol. 22, Oct. 1998, pp. 460-473 ("A10") (study began with 7 male subjects & 2 female subjects; data presented from only 4 males and 1 female); and Buridi, A., Corman, L., and Redinger, R., Hypokalemic Nephropathy and Nephrogenic Diabetes Insipidus Due to Excessive Consumption of a Soft Drink, Southern Medical Journal, Vol. 91, No. 11, 1998, pp. 1079-1082 ("C7"); Spiehler Rep. at 7.

[12] A5 and A10 were done at the same laboratory, Addiction Research Center in Baltimore, MD. Spiehler Rep. at 7.

It is outrageous that DOT is seeking to impose these potentially career ending, novel scientific cutoffs, on 8.34 million employees[13], on the basis of relevant research data from only eight men and two women. Clearly, such limited studies are scientifically and statistically inadequate to support DOT's proposition that urine with creatinine and specific gravity at such levels cannot be human urine. See Spiehler Rep. at 9.[14]

Many of the remaining studies -- none of which actually measured specific gravity and creatinine in the same specimen[15] -- do, however, confirm that certain individuals' urine did measure at or below each of the proposed "substitution" cutoffs. In nine different studies, 20 subjects had urine whose specific gravity fell

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[13] DOT states that its mandatory testing program touches some 8.34 million employees working for about 673,413 employers. NPRM, 64 Fed. Reg. 69093.

[14] The inadequacy of the data was also apparently noted by government advisor, Dr. Yale H. Caplan, who, in a presentation to laboratory inspectors in late 1999 entitled "The Urine Specimen Defined as Substituted" (funded by SAMHSA) nonetheless supported the new cutoffs. See presentation handout, Attachment 3, hereto, at pp. 3-4. Dr. Caplan is a member of the Drug Testing Advisory Board of which Mr. Stephenson is the Chair.

[15] Some of the studies presented general data or background information on drug testing, kidney function, and excessive water consumption without measuring subjects' creatinine and specific gravity. In other studies only one of the parameters was measured in a given subject, and the other parameter was either not tested or another laboratory test was substituted. Finally, some studies took creatinine and specific gravity measurements but did not "pair" the measurements with a specific subject.

below DOT's "substitution" cutoff.[16] In four studies, nine subjects' urine had creatinine levels at or below the proposed "substitution" cutoff level.[17]

Some of the research was constructed in such a way so as to preclude study on the questions that would be relevant for the proposed regulations. For example, in Abbott, K., Barr, J., Fasciano, A., and Gouge, S., Evaluation of Gender Differences in Urine Specific Gravity and Serum Electrolytes in Response to Varied Fluid Intake and Ibuprofen Use, Military Medicine, Volume 158, No. 3, 1993, pp. 131-135 ("B7"), the population -- a group of soldiers in Desert Storm -- were screened prior to selection as subjects, and those individuals with a specific

[16] Specific gravity at 1.000 was reported in 12 subjects and 12 specimens in the following studies: A10; Homer, G.M., and Born, B., A Discussion of Creatinine Analysis in Single Collection Urine Specimens, Journal of Forensic Sciences, Vol. 38, 1993, pp. 501-502 ("B5"); Vieweg, W.V.R., David, J.J., Rowe, W.T., Peach, M.J., Veldhuis, J.D., Kaiser, D.L., and Spradlin, W.W., Psychogenic Polydipsia and Water Intoxication – Concepts that Have Failed, Biol. Psychiatry, Vol. 20, 1985, pp. 1308-1320 ("C8"); Rinard, G., Water Intoxication, American Journal of Nursing, 1989, Vol. 89, pp. 1635-1638 ("C17"); Frizzell, R.T., Lang, G.H., Lownce, D.C., and Lathan, R., Hyponatremia and Ultramarathon Running, JAMA, Vol. 265, No. 6, Feb. 1986, pp. 772-774 ("C20"). Specific gravity of 1.001 was reported in 8 subjects and 25 specimens in the following studies: George, S. and Braithwaite, R.A., An investigation into the extent of possible dilution of specimens received for urinary drugs of abuse screening, Addiction, Vol. 90, 1995, pp. 967-970 ("A2"); A10; Nickman, S.L., Buckler, B.M., and Weiner, L.B., Further Experiences with Water Intoxication, Pediatrics, Vol. 41, 1968, pp. 149-151 ("C22"); and Okura, M., and Morii, S., Polydipsia, Polyuria and Water Intoxication Observed in Psychiatric Inpatients, Tokushima Journal Exp. Med., Vol. 33, 1986, pp. 1-5 ("C23").

[17] Nine subjects had creatinine reported at or below 5 mg/dL in 10 specimens in the following studies: A2; Lafolie, O., Beck, O., Blennow, G., Boréus, L., Borg, S., Elwin, C.E., Karlsson, L., Odelius, G., and Hjemdahl, P., Importance of Creatinine Analyses of Urine When Screening for Abused Drugs, Clinical Chemistry, Vol. 37, No. 11, 1991, pp. 1927-1931 ("A3"); C8 and A10.

gravity of less than 1.020 were excluded. Obviously, the absence of data below the proposed cutoffs in such a study does not support the proposition that human urine cannot have specific gravity levels below the threshold.

Likewise, the study of Park, J., Park, S., Lho, D., Choo, H.P., Chung, B., Yoon, C., Min, H., and Choi, M.J., Drug Testing at the 10th Asian Games and the 24th Seoul Olympic Games, Journal of Analytical Toxicology, Vol. 14, March/April 1990, pp. 66-72 ("A6"), provides no support for the proposed cutoffs. This paper discusses the testing methods for the Seoul Olympic Games and provides urine density readings for approximately 1600 athletes. The data was not paired with specific urine samples and the readings were not tied to any measurements of creatinine. Moreover, the population of Olympian athletes suggests little likelihood of comparable muscle mass (and therefore comparable levels of creatinine) to that of the general population.[18]

It is clear that DOT has identified no body of representative data on which to make its determinations. The research relied upon is of little value and certainly fails to provide scientific substantiation for the contention that an extremely hydrated individual, over the course of a long, trans-meridian flight cannot exceed the proposed cutoffs. While we do not contend that large

[18] Another study involving Olympic athletes -- these from the Calgary games -- likewise presents limited data (no creatinine measures) from an unrepresentative subject population. See Chan, S.C., Torok-Both, G.A., Billay, D.M., Przybyski, P.S., Gradeen, C.Y., Pap, K.M., and Petruzelka, J., Drug Analysis at the 1988 Olympic Games in Calgary, Clinical Chemistry, Vol. 37, No. 7, 1991, pp. 1289-1296 ("A7").

numbers of employees are likely to have true creatinine and specific gravity levels at or below the 5 mg/dL and 1.001 levels, respectively,[19] it is certainly possible that an extremely small percentage of employees may, on occasion, produce ultra-dilute urine. But a fraction of a percent of the millions of employees governed by these rules translates into a very real number of persons who stand to lose their careers if such cutoffs are implemented.

In sum, there is insufficient data on which to implement a rule that ends the career of an employee merely because on one occasion his or her urine measures at or below 5 mg/dL with creatinine at or below 1.001. The proposal to measure the levels of creatinine and specific gravity in employee urine is a misguided attempt to ferret out dilute urine and not address the real issue of illegal drug use. In our view, the best tools for detecting any rare cases of urine

[19] The levels reported in the studies are based on purportedly accurate measurements, as opposed to the "validity" testing methodology that is currently taking place under the "guidelines," and the even less protective procedures proposed in the NPRM, each of which have the potential to be grossly inaccurate. See pp. 23-24, supra. We do believe that some of the employees currently charged with "substituting" their samples have likely had "dilute" (or ultra-dilute) urine whose measurements were distorted by less than fully accurate screening tests. See Spiehler Rep. at 8-9.

substitution are those contained in the current procedures under which urine specimens are scrutinized and temperature readings are taken.[20]

II. DIRECTLY OBSERVED AND MONITORED COLLECTIONS

In these proposed regulations, DOT seeks to impose directly observed urine testing in a significant number of circumstances, without any true justification. Being required to urinate under the nearby and watchful eye of a stranger, who is directly observing the process, requires an employee to submit to an extremely intrusive search that greatly impinges on the employees' privacy rights. Searches such as these are <u>not</u> the kind that have survived judicial scrutiny nor would they meet the balancing of interests test that courts have employed in reviewing legal challenges.

Instead, DOT has skewed the balance against employee rights and is seeking to treat employees as malfeasants in various, unfounded circumstances. Under the NPRM, employers would be required to subject employees to directly observed testing where a test was canceled because a split sample was unavailable or could not be analyzed; or the specimen was found to be unsuitable by the laboratory and the employee was unable to provide a medical

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[20] Should DOT reject our position and insist on mandatory testing for urine dilution by testing for creatinine and specific gravity, it should not deem urine with creatinine ≤ 5 mg/dL and specific gravity of ≤ 1.001 as "substituted" but instead define it as "ultra-dilute." Individuals with such urine should not be automatically treated as rule violators, but could be subject to an unannounced, directly observed test (after MRO review, and after appropriate supervisory personnel have concurred in that decision). Such testing should be for the purpose of detecting controlled substances and not to assess urine dilution.

reason (or prescription) explaining the unsuitable analysis. In these instances, DOT is presuming employee fault and would strip individual rights, despite the fact (and even DOT acknowledgment) that such problems may be largely attributable to the laboratories.

Split specimen analysis, as discussed earlier (see pp. 11-13, supra), is a legislated protection intended to assure that an employee not be falsely branded as an illegal drug user due to specimen mishandling or laboratory error. It is for this reason that a drug test certified as positive by one lab, must be canceled if it cannot likewise be confirmed as positive by analysis of the split at a second, independent lab. A failure of the split to confirm a positive drug test indicates a problem with the laboratory or collector, not the employee. But instead of exonerating the employee, DOT seeks to further invade individual privacy.

This is wholly unwarranted particularly in light of DOT's experience that "the overwhelming majority of test cancellations related to split specimens result from collection or logistical problems (e.g. collector fails to collect the split specimen, a split specimen is lost or leaks in transit)." NPRM, 64 Fed. Reg. 69082. The solution is to ensure that the split sample procedures are properly followed and to ensure that service agents comply with the rules -- not to penalize innocent employees.

Similarly, with respect to "unsuitable" samples, DOT fails to recognize that there are many reasons, other than employee misconduct, why a sample may not be suitable for testing. Some known examples include improper specimen sealing, specimen leakage in transit despite proper packaging, laboratory spillage and the inability of certain immunoassay screening tests to analyze samples at certain pH levels. Spiehler Rep. at 7. It is wholly unjustified to shift the burden to employees, presume their guilt, and subject them intrusive searches merely because of the infrequent but inevitable problems with collecting, shipping and analyzing specimens.

We also object to the proposal to allow employers to subject employees to directly observed testing if the employees' prior urine sample was found to have a specific gravity of < 1.003 and creatinine of < 20 mg/dL, characterized in the NPRM as a "dilute" sample.[21] There is no need or justification for such intrusive searches of these individuals. As we mentioned previously, DOT has presented no evidence that any significant number of employees are adding water to, or substituting their samples. We simply do not believe that there is a problem of any magnitude justifying this approach.

Moreover, neither drinking water, nor having dilute urine is an offense and should not be treated as such. And while a very small percentage of individuals may have "ultra-dilute" urine, a greater number can be expected to have "dilute" specimens. Even the limited data relied upon by DOT in NLCP#1 indicates that dilute urine occurs with some frequency. The available paired data

[21] If DOT continues to use the term "dilute specimen" in the final rules, its definition should not be pejorative and not imply any employee misconduct merely because an employee's creatinine and specific gravity levels fall below any DOT established parameters.

showed that even before the experiment began, six percent of the subjects had urine meeting the NPRM "dilute" standard. See Spiehler Rep. at 8.

This is consistent with Dr. Spiehler's assessment, that the likelihood that the average person's spot urine will have less than 20 mg./dL of creatinine is approximately five to six percent. Id. For flight crew members who consume a lot of water on long flights, the frequency of "dilute" urine will be even greater. Based upon her review of the hydration studies cited in NLCP #1, Dr. Spiehler concludes that drinking more than a liter of water during a period of two to four hours increases the likelihood that a spot urine test of that person's urine will meet the "dilute" standard from 5-6% to 32-44%. Id. That percentage may be even greater for female employees. But employees should not be singled out to their employers and subject to humiliating tests, merely because they consume water in an aircraft cabin.

The NPRM also seeks to vastly expand the collectors' authority to directly search employees, make important judgment calls about employees' motivations, and directly observe employee urination. The collectors are to have employees empty their pockets and remove their boots in order for the collector to determine whether there are any materials that "could be used" to adulterate a sample, and if so, whether an employee brought them "inadvertently" or "appears to" have brought them "with the intent to alter the specimen." NPRM, 64 Fed. Reg. 69102 § 40.61(f). If in that collector's sole discretion, he finds the employee had bad "intent" that same collector is to order the employee to provide a urine sample under his direct observation.

These provisions would give collectors tremendous discretion and invite arbitrary orders requiring employees to submit to degrading, observed testing. An employee might be deemed to have the "intent" to alter the sample if a pocket-sized bottle of hand disinfectant, packets of salt leftover from lunch, a travel-sized shampoo bottle or cologne was discovered in the employee's pocket. Subjecting employees who may have otherwise innocuous items on their person to embarrassing and unfounded searches should not be permitted.

While we do not endorse all the provisions of the current regulations,[22] DOT has shown no reason why the carefully defined standards and safeguards for limited, directly observed testing should not remain. Under the current regulations, <u>the personal observations of the collector</u> can justify directly-observed testing in only two specifically delineated instances.[23] Moreover, even in such cases, "[a] higher-level supervisor of the collection site person, or a

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[22] As discussed previously, we do not support treating employees with dilute samples as guilty of wrongdoing and, accordingly, object to the provision in the current regulations that would permit directly observed testing of employees whose last urine sample was reported to have a specific gravity of less than 1.003 and a creatinine concentration below .2g/dL [or 2mg/dL]. 49 C.F.R. § 40.25(e)(2)(ii).

[23] Those circumstances are: (1) where the temperature of the urine specimen is out of range <u>and</u> at undue variance with the body temperature (or the employee refuses to provide a non-rectal, temperature reading); or (2) the collector "observes conduct clearly and unequivocally indicating an attempt to substitute or adulterate the sample (<u>e.g.</u>, substitute urine in plain view, blue dye in specimen presented, etc.)." 49 C.F.R. § 40.25(e)(2).

designated employer representative, shall review and concur in advance with any decision by a collection site person to obtain a specimen under the direct observation of a same gender collection site person . . . ." 49 C.F.R. § 40.25(e)(3). In our view, there is no basis for further eroding employees' rights by mandating directly observed testing, expanding the circumstances in which such testing may occur, and eliminating the requirement of proper supervisory concurrence.

DOT also seeks to lessen employee privacy rights by loosening the current stringent limitations on "monitored" testing. Currently, individual privacy is the rule and monitored testing (where the collector stands nearby and listens closely to the sounds of urination) occurs only in "the exceptional event" that the collection site is not accessible, and there is an "immediate" need for testing, such as in a post-accident situation. 49 C.F.R. § 40.25(f)(9). The proposed rules would permit "monitored" testing merely if a site fully meeting all the privacy requirements "is not readily available." NPRM, 64 Fed. Reg. 69103 § 40.69. Employee privacy should not be so readily or easily disregarded. Rather, it must remain the rule and exceptions granted only in "exceptional" and exigent circumstances.

III. PROTECTING EMPLOYEES FROM ADVERSE CONSEQUENCES PRIOR TO COMPLETION OF THE MRO REVIEW PROCESS -- THE "STAND DOWN" ISSUE

We strongly oppose any change in the regulations that would allow an MRO to identify an employee to an employer as having a positive drug test, and allow the employer to remove that employee from service ("stand down"), prior to completion of the verification process. The process of verifying that a laboratory certified positive drug test is due to the use of illegal drugs as opposed to an authorized prescription or other legitimate medical explanation is an essential employee safeguard. It is intended to protect employees from being falsely charged and unfairly treated as illegal drug users.

If MROs are allowed to report, unverified positive results to employers, this protection would be substantially undermined. Providing such information to employers would forever label the affected employees as drug users, resulting in a stigma from which they would never be free. It is also likely that the reason for the employee's removal from service would be known or surmised by other employees and supervisory personnel, further tarnishing the employee's reputation.

The regulations have and must continue to protect against such adverse effects. Nor is there any good reason to eliminate this limited employee protection.[24] As DOT has recognized, there have been no known instances of any adverse safety consequences due to compliance with the existing provisions over the course of the millions of tests conducted since the program's implementation. NPRM, 64 Fed. Reg. 69083. There is simply no justification for eroding this limited employee protection at this juncture.

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[24] The protection is limited because DOT does require employees whose drug tests are verified as positive by the MRO to be reported as such prior to analysis of the split sample. Thus an employee who is exonerated because the split does not confirm the positive test result may suffer the potentially adverse effects of the prior report. DOT should not further lessen the rights of employees.

IV. GREATER ACCOUNTABILITY OF SERVICE AGENTS SHOULD BE ENSURED AND APPROPRIATE ACTION TAKEN AGAINST THOSE FAILING TO COMPLY WITH REGULATORY AND PROCEDURAL REQUIREMENTS.

We support the proposal to make "service agents" more accountable and provide greater assurance that such individuals or entities comply with the legal and regulatory requirements, especially the Part 40 procedures. We agree that there should be a means by which service agents who violate the regulatory provisions can be precluded from continuing to perform such functions. We do not think it sufficient to have agents "self certify" that they have or will comply with Part 40. DOT has already seen egregious instances of noncompliance. Cases such as those, and even less serious violations, should be subject to regulatory oversight and sanction. We further believe that any procedure that is implemented should provide a timely means by which such problems can be promptly addressed.

It is also important to reaffirm, as DOT states, that it remains the employers' responsibility to ensure that the service agents they hire comply with the regulations. NPRM, 64 Fed. Reg. 69099 § 40.11. Employers too should remain subject to regulatory review and sanction if they fail to provide sufficient oversight over the service agents with whom they contract.

V. THE IMPORTANCE OF CERTIFICATION AND TRAINING REQUIREMENTS FOR COLLECTORS, MROS AND SAPS

A. BAT (AND STT) AND COLLECTOR TRAINING AND QUALITY ASSURANCE

The mandatory training to proficiency and retraining requirements for Breath Alcohol Technicians ("BATs") and Screening Test Technicians ("STTs") are important and should be maintained. We agree that similar training requirements should also be implemented for Urine Collectors. It is especially important to have retraining and demonstrated proficiency for such personnel when they have made any mistake that results in the cancellation of a test.

It is important, as the NPRM requires, that the technician document any errors in the testing process, and be required to provide copies of such documentation to the employee and the employer. The collector should be instructed to carefully document any procedural errors (including items not identified as "fatal flaws") on the CCF. However, it should also be acknowledged that some errors may not be recognized at the time the test is administered (or the specimen collected) by either the technician (the collector) or the employee, and hence may not be either corrected or contemporaneously documented.

We agree with the requirement that documentation of training and retraining be retained by the technicians and collectors personally, and also by the party employing the technician or the collector. However, such documentation should also be provided to the employer, who should likewise be required to maintain it. In addition to training records, all records of technician or collector error, specifically identifying any errors causing the cancellation of any tests, should be required to be similarly maintained. It is important for employers to be responsible for keeping relevant information, because the employer can provide it most readily to the employees. Moreover, the regulations should explicitly state that all such information shall be provided to covered employees or their designated bargaining representative, upon request.

Additionally, we strongly agree with the requirement that the employer provide a phone number contact for the technician or collector to be able to reach a supervisor if any problem or question arises during an employee test. This will be of mutual benefit and can help prevent reports of "refusals" when questions or problems arise.

B. MRO TRAINING AND RESPONSIBILITIES

We support the proposed requirements for MRO certification and training. We think it is particularly important for each MRO to attend "recurrent" training, that is retraining at least once every two years that reviews the responsibilities under the applicable regulations, and any modifications or changes made to them. In our sector, the MROs are certified and already participate in such training. We think these minimum requirements should be formalized and that "self-certification" should not be a substitute for them.

Such training should highlight the MROs' responsibilities to act as "an independent and impartial 'gatekeeper' for the accuracy and integrity of the drug testing process" and obligation to "provide a quality assurance review of the drug testing process for the specimens under [the MRO's] purview." NPRM, 64 Fed. Reg. 69109 §§ 40.123(a) and (b). We have stated earlier our view that this reviewing role necessitates the consideration of relevant, independent evidence and should not be limited to the CCF. See discussion pp. 17-19, supra.

We are also concerned that in some recent cases MROs have appeared to fall short of the appropriate independence and dispassion contemplated by the regulations, and performed as the hand of the employer – rather than a neutral, reviewing entity. It is important that such responsibility be emphasized in the regulations, and included in retraining programs.

C. SUBSTANCE ABUSE PROFESSIONALS

We support the requirements for training and recurrent training for Substance Abuse Professionals ("SAPs"), but think that such training must be accomplished directly and that self-certification does not suffice. While ensuring professional competency is essential and accreditation can be helpful, we have concerns about DOT relinquishing control of the process and such oversight being limited to one domestic certifying body. Accreditation by the National Association of Alcoholism and Drug Abuse Counselors Certification Commission ("NCCA") is expensive. It is important that any fees involved in this process be established, and maintained, at reasonable levels. We are concerned that the existing cost structure might keep qualified individuals and entities away from the DOT drug testing program. It is essential that DOT directly approve any accreditation decisions as well as ensure that fees are reasonably limited.

With respect to the SAPs' functions, it is important that they have access to the same information about employees' drug tests as the MROs. Information, such as the quantitative levels of prohibited substances can be extremely useful in judging the severity of individuals' problems and determining the appropriate level of treatment. It can also help avoid conflicts between SAPs and Independent Medical Sponsors.

Additionally, the regulations must provide a means by which an employer can utilize another SAP if it becomes apparent that the one involved has not been through, performed the adequate level of review, or has performed work which is otherwise deficient. ALPA's Aeromedical staff is aware of instances in which this has occurred. For this reason, we recommend that in such cases, where both the employer and employee agree, an evaluation by another SAP should be permitted. We do not suggest this in order to provide an avenue of review or appeal, but rather as a means of quality assurance to assure a through and accurate evaluation.

VI. COLLECTION PROCESS

The regulations provide an employee who is unable to immediately provide the requisite quantity of urine ("shy bladder") three hours within to consume an additional quantity of water and provide the necessary sample. While the inability to provide sufficient urine may be due to a medical condition, in many circumstances it is because the employee happened to relieve himself or herself soon before notification of the test. In either case, the regulations should permit employees the full three hours in which to produce the appropriate amount of urine, and not cut short the test prior to that time period.

An employee who fails to produce the requisite amount is at risk of being deemed to have "refused" to test, and has the consequent risk of losing a career. Such individuals should be given the full opportunity to determine the pace at which they drink water and attempt to provide the sample, and be given the opportunity to have the water eliminated through their system.

Employees subject to medical evaluation for being unable to produce the required amount of work must be evaluated by a doctor with appropriate expertise, either a urologist or a nephrologist. The suggestion in the NPRM that such evaluation may be performed by the MRO, or any other doctor, should be rejected. Where employees stand to lose their careers unless they demonstrate a medical condition interfering with the ability to produce urine, they should be entitled to an examination by a doctor with the appropriate experience and expertise.

VII. IT IS ESSENTIAL THAT THE REGULATIONS ENSURE THAT EMPLOYEES AND UNIONS GET ACCESS TO RELEVANT INFORMATION.

In a number of cases we have had difficulty obtaining important and relevant information. The regulations should make clear the obligation of employers and laboratories to provide such information. The employer's obligation to procure and provide to employees information in the possession of its service agents -- such as MROs -- should be made explicit. We also think the regulations should reiterate DOT's authority and willingness to take action against employers that fail to comply with their regulatory obligations in this regard.

The regulations should identify the broad categories of data that must be provided, as well as identify with specificity examples of the particular data such information includes. The obligations of the employer and the service agents to provide all information regarding employee drug and alcohol tests; allegations of drug and alcohol misuse; test results, analyses and reports; laboratory records, including quality control and operating procedures documentation should be explicitly asserted. Additionally, it is necessary for employees and their union representatives to have access to statistical data regarding all test results (drug and any "validity" tests) and quality controls.

When employers send blind samples to the laboratories, they should be required to maintain records of the analyses of those samples and provide them upon request to covered employees, or their bargaining representative. If an employer's blind testing is done by a consortium, the employer should remain responsible for providing that information, upon request, to any covered employee or bargaining representative. Laboratories should also be required to maintain information about any failed blind tests, the cause of the error and the corrective action taken, and provide such information upon request to covered employees, or their bargaining representative.

The regulations should also clearly state that employees and their bargaining representative shall have access to laboratory quality control data, specifically the items the labs are required to maintain for two years as set forth in the NPRM, 64 Fed. Reg. 69108 § 40.109 (quality assurance and quality control records; procedure manuals; performance records on performance testing; and results of certification inspections.) It should be clearly stated that such quality control data includes all laboratory internal and external quality control data, as well as laboratory Standard Operating Procedures ("SOP").

The regulations should also require that the statistical summaries that the laboratories are required to provide to employers on a semi-annual basis (NPRM, 64 Fed. Reg. 69108 § 40.111(a)) also should be made available to covered employees and their bargaining representatives on the same terms and conditions as to the employers.

VIII. THE IMPORTANCE OF MAINTAINING AND EXPANDING THE PROTECTION OF BLIND SPECIMEN TESTING AND OTHER QUALITY ASSURANCE

Blind specimen testing is an essential quality assurance safeguard for the drug testing program and should be maintained. This is a key check on the accuracy of all aspects of the testing process, but especially the laboratory handling and analysis. The knowledge by laboratory personnel that they are subject to blind specimen testing, as well as the actual check of such samples, make this a vital aspect of the testing program. It is also important that if DOT implements "validity" testing, that blind specimens include samples with whatever compounds or solutions are to be included in the "validity" testing program. We strongly oppose any weakening of this important protection.

The requirement of Quality Assurance Plans ("QAPs") for evidential breath testing devices ("EBTs") should also remain intact. These plans are important because they specify, among other things, the minimum frequency at which EBTs must be serviced and subjected to external calibration checks. If DOT eliminates the requirements for QAPs it should include such standards and requirements in the regulations. It is essential that employers be required to maintain testing equipment in accordance with the proper maintenance and servicing schedules.

IX. TESTING FORMS AND MATERIALS

We agree that a "firewall" should be maintained between DOT and non-DOT tests. This is to ensure that all testing done under DOT mandate be in accordance with the required procedures and protections. Requiring that such tests use only DOT forms is a way to facilitate such compliance and avoid unnecessary problems. Should DOT decide that use of a non-DOT form is a "correctable" error, we submit that the burden should then shift to the employer to demonstrate that all DOT required procedures were properly followed.

DOT has asked for comment on the potential use of electronic records and signatures. While use of such procedures may have the potential for increased efficiencies. It may also present many safety and security risks. In our view, a specific proposal is necessary in order to make meaningful comments. Should DOT wish to consider any such options, they should be presented pursuant to notice-and-comment rulemaking.

Finally, we do commend DOT for reorganizing the rules and presenting them in a much more "user-friendly" manner. This new organization should make the regulatory requirements easier to identify and understand.

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Dated: April 7, 2000

Report of Vina R. Spiehler, Ph.D., DABFT

Forensic Toxicologist

DATE: April 6, 2000

TO: Air Line Pilots Association, International

FROM: Vina Spiehler

RE: **The Proposed Changes to DOT 49 CFR Part 40**

Summary

The proposed changes as regards dilute, adulterated and substituted samples do not meet the standards employed by DOT for drug testing. Unlike the DOT regulations for drug testing the proposed DOT regulations for specimen validation testing do not meet the requirements for forensically acceptable tests. The definitions of SAMSHA PD35 are transferred to the DOT Regulations but the safeguards of SAMSHA PD37 are not included. Screening and confirmation tests should be specified and required for specimen validation testing just as they are for drug and alcohol tests.

Further, reconfirmation of validation test results on split samples is not provided and should be. Reconfirmation by another laboratory is an important check on a laboratory's methods, procedures and accuracy as no one is absolutely error-free and simply repeating a test will not reveal flaws or failure in the testing procedure.

The scientific papers cited as the basis for the proposed rules by SAMSHA NLCP February 14, 2000 document are inadequate from which to conclude that human urine cannot have specific gravity of ≤ 1.0010 and creatinine ≤ 5.0 mg/dl. The scientific studies presenting paired data for creatinine and specific gravity are inadequate as they two (of four) of them come from only one laboratory (Addiction Research Center, Baltimore, MD) and use too few subjects (18 total, of which only three were female). The cutoffs for adulterants (nitrites) are supported by a single study available in the peer reviewed literature.

Any cutoffs for ultra-dilute specimens should be expressed to the first decimal beyond the value, e.g. if the cutoff is less than or equal to five and 1.001 then the cutoff should be expressed as ≤ 5.0 mg/dl creatinine and ≤ 1.0010 specific gravity.

Below are recommendations for alterations in the Proposed Changes to 49 CFR Part 40 which I believe are required to provide protections in specimen validation testing equal to those currently applied to employee urine drug testing.

Discussion

I have reviewed the current DOT 49 CFR Part 40, the 49 CFR Part 40 Proposed Rules published in Federal Register Thursday December 9, 1999, the SAMSHA guidance documents 35 and 37, the SAMSHA NLCP Update memo of February 14, 2000 and read and reviewed all of the 45 papers cited in the NLCP 2/14/00 Update, the package inserts for screening tests and literature reports on confirmation tests for analytes mentioned in the Proposed Rules, the outline of Dr. Yale Caplan's presentation SAMSHA 277-99-6033 as well as other relevant literature and scientific studies.

The following discussion reviews the standards of practice in forensic toxicology, the scientific basis for confirmation (Bayes law) and a brief review of screening and confirmation methods for specimen validity tests. That is followed by a discussion of the need for studies to provide a scientific basis for the proposed specimen validation criteria and conclusions of published studies on the predictive value of current tests.

Forensic Standards for Scientific Tests

American Academy of Forensic Sciences (AAFS) Policies on Confirmation: In 1976 the AAFS Toxicology Section adopted a formal policy that no positive screening immunoassay test result should be reported without confirmation by a second procedure based on a different chemical or physical property of the analyte. This policy was written by Prof. Kurt Dubowski and voted on at the annual meeting. This was a specific application of the principle of confirmation quoted in every textbook on forensic toxicology since the 19th century. "We think it is the duty of the toxicologist always to employ the various corroborative tests; by omitting to do this, his otherwise excellent evidence may be materially weakened" J.J. Reese, *A Manual of Toxicology* 1874 quoted in p 151 Cravey and Baselt *Introduction to Forensic Toxicology*. More recently: "For a substance to be reported as positive, at least two different analytical techniques must be used. The use of a second or confirmatory technique is a fundamental principle in forensic toxicology." B. Levine. *Principles of Forensic Toxicology*, 1999, page 7.

AAFS/SOFT Forensic Toxicology Laboratory Guidelines. These guidelines were adopted by the Society of Forensic Toxciologists and by the Toxicology Section of the American Academy of Forensic Sciences in 1991. They have further been adopted for the AAFS/SOFT Laboratory certification program for forensic laboratories. The 1997 version of the Guidelines states: "As a general matter of scientific and forensic principle, the detection of drugs and other toxins should be confirmed whenever possible by a second technique based on a different chemical principle." Page 7, Analytical Procedures, Confirmatory Tests.

The proposed changes to 49 CFR part 40 provide confirmation for drugs and drug metabolites but not for specimen validation tests.

Probability and Predictive Value. The scientific basis for the principle of confirmation is that the consistent, corroborative findings of independent tests of the same value or fact increases the probability that the finding is true. In mathematical terms this is known as Bayes Law which allows the probability that a hypothesis is true to be calculated from the known error rate (or truth rate) of the test of the hypothesis. If more than one test is performed and the two tests are independent, then the probabilities can be combined to give a higher probability that the finding was true.

The independence of the two tests can be analyzed using principal component analysis. This has been done in forensic toxicology and the results are that performing the second test on a fresh aliquot of the primary specimen and using a procedure for the second test based on a different chemical or physical property of the analyte will insure that the two tests are independent. For most drug tests in urine the combination of an immunoassay positive and a GC/MS positive results in a probability of greater than 99.9% that the drug or drug metabolite is present in the urine specimen (Spiehler et al 1988).

From my experience testifying as a scientific expert, I am aware that the US Supreme Court in Daubert v. Merrell-Dow and subsequent cases has identified criteria that should be present when scientific evidence is offered as evidence in court. Scientific evidence should fulfill the following criteria:

a. It should be relevant to the case, i.e. will assist the trier of fact

b. The method employed should be scientifically testable

c. The method validation should have been published in a peer-reviewed journal

d. The error rate should be known

e. The method or procedure should be generally accepted by the scientists in that field. (Frye criteria)

These criteria are met by the SAMSHA Mandatory Guidelines and DOT 49 CFR part 40 for drug and drug metabolite tests but the proposed changes do not meet the requirement *d.* that the error rate must be known for specimen validation testing or *e.* that the method be generally accepted because it does not provide for confirmation testing. Confirmation testing is a requirement in the practice of forensic toxicology.

Prevalence The predictive value of a positive test result is a function not only of the error rate of the test (diagnostic sensitivity and diagnostic specificity) but of the prevalence of the condition in the population being tested. For example, for a test with 99% sensitivity and 99% specificity, the predictive value for a positive result in a population in which only one out of a thousand persons has the condition being tested for is only 9% (Galen and Gambino 1975). The predictive value of the drug tests as calculated by manufacturers in method validation using balanced populations with half positive and half negative specimens is much higher than the predictive value of actual test populations in which the prevalence of drug use is less than 10 percent or even less than one percent (Ferrera 1994).

SAMSHA Mandatory Guidelines establish procedures for drug and drug metabolite testing which meet the forensic standards described above. The regulations require that specimens positive by an initial screening test be confirmed by a quantitative confirmation test. The screening test must be immunoassay and the confirmation test must be GC/MS. This insures that the two tests are carried out by two different methods based on different chemical and physical properties of the drugs and drug metabolites. For illegal drugs of plant origin a positive screening test by immunoassay **and** a positive confirmation test by gas chromatography/ mass spectrometry (GC/MS) increases the probability that a positive is a true positive to 99.9% or better. For synthetic drugs such as the amphetamines two different immunoassays and two different chromatographic procedures are required to achieve the same degree of scientific certainty. These procedures are currently followed in employee drug testing.

In my opinion it is unlikely that a single colorimetric screening test for creatinine, nitrite, specific gravity, glutaraldehyde or pH on urine has a predictive probability of greater than 75%. Repeating the test or using a dip-stick version of the same reaction as a "confirmation" would not increase the probability that a positive result is a true positive because the second test is not independent and would be subject to the same errors and interferences as the first. Combining screening tests for specific gravity with screening tests for creatinine is not appropriate confirmation of dilution, substitution or adulteration as there would be no accurate confirmation of the initial analyte value and the literature suggests that the two are not independent tests of urine dilution (Vieweg et al 1985 C8).

How Forensic Standards could be incorporated into Validity Testing

1. Require at minimum two level testing, an initial or screening test followed by confirmatory quantitative test based on a different chemical or physical property of the analyte for specimen validity tests for creatinine, specific gravity, pH, nitrite and other adulterants. This insures that the probability that the final result is correct (true positive, true adulterated or true ultra-dilute) is increased to an acceptable degree of scientific certainty.

2. Require that the screening tests used for employee urine drug testing be FDA cleared (510(k)) or FDA approved (PMA) for detection of adulteration and dilution or that the diagnostic sensitivity (true positive rate), diagnostic specificity (true negative rate) and predictive value for detection of adulteration and dilution meet FDA standards. SAMSHA and DOT regulations (DOT 49 CFR Part 40 Sec. 40.29e.(1)) currently require that immunoassays used for screening for drug or drug metabolites must be FDA cleared (510(k)) or approved (PMA). This would meet the requirement of the Federal Rules of Evidence Rule 702 that the error rate be known. The tests currently used for specimen validation screening tests were approved (or grandfathered in) by FDA for clinical uses (such as testing for renal function or identifying bacterial infection) at different cutoffs, not for specimen validation at the cutoff levels in the proposed DOT changes to 49 CFR Part 40.

3. Allow reconfirmation of the results on the split specimen by an independent laboratory. If stability is of concern this could be done immediately on verified adulterated or ultra-dilute specimens. Reconfirmation need not be at the initial cutoff for nitrites or other adulterants. Reconfirmation must be at the same cutoffs for creatinine, specific gravity, pH and osmolality. Spierto et al 1997 have reported that urine creatinine concentration is unaffected by storage time and temperature.

Screening Tests and Confirmation Tests. Generally the tests currently used for creatinine, specific gravity, pH, nitrites, glutaraldehyde and other adulterants are non-specific colorimetric tests suitable for screening. They are generally performed either as dip-sticks or as liquid reagents in the same automated analyzers used for the drug immunoassay screening testing. Reagent-strip or dip-stick tests are available from a number of companies: Chimera Research and Chemical, Inc., Asheville, NC (800-749-4537) markets dip-stick (AdultaCheck) and liquid reagents (AD Perfect) tests for creatinine, nitrite, bleach, chromate, glutaraldehyde, specific gravity, pH, and oxidants. Boehringer Mannheim Corporation, Indianapolis, IN makes the ChemStrip 6, 7, 8, 9, 10 with SG. DRI-Microgenics, Pleasanton, CA (800-354-8839) makes liquid reagents for detection of nitrites, chromate, specific gravity, pH and creatinine. Axiom Diagnostics, Tampa, Fl (888-837-8783) markets tests for adulterants.

The cutoffs for nitrites are supported by a single study available in the peer reviewed literature (Urry et al 1998). FUDT laboratories are currently using screening tests for pH, nitrite, glutaraldehyde, chromium, and other adulterants. Unfortunately in many cases they are checking the positive results by merely repeating the test. True confirmation tests exist for creatinine, nitrite, glutaraldehyde, chromium and other possible adulterants.

Confirmation methods for analytes such as creatinine, nitrite or gluteraldehyde are generally chromatographic. For example, tests appropriate for confirmation of creatinine include Yang 1998, Shirao et al 1997, Yasuda et al 1997; for nitrites, Singh et al 1999, EPA method 353.2; for glutaraldehyde, Samson et al 1993. BioRad Laboratories, Hercules, CA, (www.bio-rad.com), Waters Corporation, Milford, MA (www.waters.com), and Shimadzu Scientific Instruments, Inc., Columbia, MS (800-477-1227) all make HPLC instruments suitable for chromatographic confirmation of creatinine, nitrites, glutaraldehyde and other small molecules and adulterants. Perkin-Elmer Sciex, Foster City, CA (508-383-7217) makes liquid chromatography-mass spectrometry instruments which are used in some of the above referenced methods for confirmation of adulterants.

Confirmation methods for properties of aqueous solutions such as pH, specific gravity and osmolality should be direct measurements of the definition property not estimates from a related or associated property. For example, for specific gravity a urine-calibrated hydrometer or accurate electronic or chain balances, for pH, a pH meter using glass electrodes and for osmolality, a freezing point instrument is available. Indirect methods are calibrated and controlled with artificial, inorganic solutions. With biological specimens estimates introduce an element of error which is often more pronounced at the low and high end values such as those employed in the Proposed Rule criteria. When the criteria are "less than or equals," any error in an indirect measurement can mean the difference between passing or not passing the test.

Off-label Uses. The test methods used by FUDT laboratories have not been approved or cleared by FDA for determination of adulteration or substitution. Those tests which are FDA approved were submitted for use in clinical diagnosis of bacterial infection, creatinine clearance from 24 hour urine collections or other measures of renal function respectively. Dr. Smith of Chimera Research Chemicals which makes the most widely used commercial tests for adulterants and substitution, testified before the SAMSHA Drug Testing Advisory Panel on October 6, 1999 that FDA clearance for the adulteration and substitution tests was obtained by the Ames Company which first marketed the paper strip tests (Ames Dip Stix, Ames Company Division of Miles Laboratories. Elkhart, IN). However the Ames paper strip tests for urine were marketed before 1974 and thus were "grandfathered" in when the FDA began to require submission of diagnostic tests.

SAMSHA Program Documents 35 and 37

The proposed changes to 49 CFR Part 40 incorporate the definitions of dilute, "substituted" and adulterated specimens released to HHS certified laboratories on September 28, 1998 and to NLCP Inspectors on October 6, 1998 (SAMSHA PD 35 1). Although analysis of specimen validation analytes and properties was voluntary, the assembled scientists at the October 1998 and subsequent meetings objected to the lack of scientific basis for the proposed measurements and their interpretation. Therefore, SAMSHA followed up in July 28, 1999 with a further notice to certified laboratories which was released to NLCP Inspectors on October 10, 1999 with guidance and criteria to improve the scientific validity of the testing (SAMSHA PD 37 2). PD 37 directed that at a minimum creatinine be measured by at least one quantitative procedure on two different aliquots; that pH and nitrites be measured by two procedures on two separate aliquots; and that other adulterants be detected by at least one procedure on two separate aliquots. PD 37 also required all specimen validity testing methods to be validated by the laboratory, to be described in the SOP and to be performed with some quality control specimens.

While some inspectors assumed that SAMSHA intended the two procedures to be based on different analytical principles, the NLCP laboratories, their experts and their attorneys have been arguing in arbitrations that that was not the intent of SAMSHA PD 37 and that two procedures may use the same methodology. Repeating the same testing method fails to meet the scientific standard for confirmation which requires a second test based on a different chemical property of the analyte. Therefore, the Part 40 needs to be explicit on this point and require that the two procedures on two aliquots be based on different chemical or physical properties of the analyte.

SAMSHA PD 37 required that results used for $\leq$ (less than or equal to) criteria must be determined to one decimal place greater than the cutoff since truncating a quantitative value is not acceptable with a $\leq$ decision point or cutoff. "In "$\leq$" scenarios, truncating a quantitative value would change the result from acceptable to unacceptable (e.g. truncating a pH reading of 3.2 to 3 or a creatinine of 5.4 mg/dl to 5 mg/dl)." The screening tests for creatinine, specific gravity and pH such as colorimetric and paper/stick tests are not capable of discriminating this level of analyte. For example they can not discriminate 5.0 from 5.3 and at times are not capable of discriminating 5 from 6 mg/dl creatinine.

SAMSHA PD 37 also specified that at a least one control in urine matrix in the acceptable range and one control in urine matrix in the unacceptable range must be analyzed with each batch of validity test specimens.

SAMSHA PD 37 directs that specimens with creatinine ≤ 5 mg/dl but with specific gravity between 1.003 and 1.019 be reported as Specimen Unsuitable: Unable to Obtain Valid Drug Test Results. Specimens with pH of < 4.5 or > 9 can be reported as Specimen Unsuitable: Unable to Obtain Valid Drug Test Results if the immunoassay test can not cope with the sample pH even though the specimen does not meet the "adulterated" criteria of ≤3 or ≥11. Under the proposed new DOT rules reporting a specimen as Specimen Unsuitable: Unable to Obtain Valid Drug Test Results must result in immediate collection under direct observation with no advance notice to the employee.

The proposed changes to 49 CFR Part 40 fail to incorporate the requirements of PD 37 for test method quality and independence which would take the first steps toward insuring that the probability of reporting a correct result meets forensic standards.

Lack of Scientific Basis for Cutoff Levels

Studied Populations. The scientific studies presenting paired data for creatinine and specific gravity which are cited as the basis for the proposed rule changes by SAMSHA in the February 14, 2000 Update document are inadequate to draw the conclusion that human urine cannot have a specific gravity of ≤ 1.001 and a creatinine of ≤ 5 mg/dl because too few individuals were studied. The total number of subjects with paired data on creatinine and specific gravity is only 18. Two of the four studies with paired data come from only one laboratory (Addiction Research Center, Baltimore, MD) and use too few subjects (16 of the 18 total subjects, of which only two were female) (Goldberger et al 1995 A5 and Cone et al 1998 A10). All of these subjects were drug users (heroin, Goldberger et al 1995 A5 and marijuana and cocaine, Cone et al 1998 A10, A11). These data may not apply to women because only two women were included in the studies which paired creatinine and specific gravity. Of these two, data was presented for only one woman since the other did not complete the study (Cone et al 1998 A10). The other two references with paired data each have only one subject (Coleman and Baselt 1997 B2, 1 male; and Buridi et al 1998 C7, one female). The Buridi et al 1998 publication is a case report, not a controlled study.

The use of reference ranges of creatinine for 24 hour urine collection (Table 1 of the SAMSHA 2/14/00 Update 1.) as reference ranges for random or spot urine concentrations is inappropriate. As is discussed in Dr. Ottinger's published commentary on the Needleman 1992 study, only the average values from random urine collections can be compared to the time-averaged 24 hour collection not individual values (Ottinger 1993). Shepard et al 1981 A4 reported an intra-individual variation for creatinine of 50% while Huestis and Cone 1998 A11 reported that the intra-individual percent coefficient of variation of creatinine ranged from 33.5% to 69.9% in individual specimens from six male subjects. Ricos et al 1994 concluded that due to this intra-individual biological variation that urine creatinine may be a poor test for diagnosis, monitoring and screening.

Many studies cited in the Update memo have only one subject. Forty-one of the studies listed in the February 14, 2000 Update did not use the combination of creatinine **and** specific gravity which SAMSHA relies on in defining "substituted" specimens. Further, the conclusion that human urine cannot measure at these levels derives from negative evidence (no instances of that particular combination were noted in a limited sample from one laboratory) when few of the studies actually looked at these variables together.

Prevalence of Dilute or Ultra-Dilute Urine Specimens. Of the studies cited by SAMSHA NLCP Update of February 14, 2000, four studies reported paired data of both creatinine and specific gravity in 18 subjects. In these subjects before experiments began, dilute urine (defined as < 20 mg/dl creatinine **and** < 1.003 specific gravity) appeared in 0.2% of the specimens and in 6 % of the subjects. However, 1.5% of the specimens and 41% of the subjects had creatinine < 20 mg/dl in normal random spot urines and would have been reported as Specimen Unsuitable: Cannot obtain valid drug test result." In the studies cited by the SAMSHA memo of Feb 14, 2000, there were 2 specimens with creatinine less than or equal to 5 mg/dl, 29 specimens with a specific gravity equal to 1.001 after drinking water and one with specific gravity of 1.000 before drinking studies began. These specimens would be reported as "Specimen Unsuitable." The incidence of "Unsuitable" tests after drinking water was 15.5% of specimens and in 100% of the subjects. All the subjects produced a spot urine with creatinine ≤ 5 or specific gravity $\leq$ 1.001 one or more times after drinking water.

The risk that a person's spot urine will have less then 20 mg/dl creatinine is 5-6% for the average person. The risk for airline crews who attempt to keep themselves hydrated during long flights will be greater. Based on the published hydration studies cited by SAMSHA, drinking more than a liter of water during a period of two to 4 hours increases the likelihood that a person's spot urine test obtained two to ten hours later will have less than 20 mg/dl creatinine and less than 1.003 specific gravity from 5-6% to 32-44%. The more water that is consumed the greater the likelihood that the urine will be dilute.

This may not apply to women because only two women were included in the water drinking studies which paired creatinine and specific gravity. Data was presented for only one woman since the other did not complete the study. Gault et al 1994 reported that creatinine and urea clearances decline in mid-menstrual cycle.

Based on the calculated theoretical limit for human urine (Caplan 1999) of 1.7 mg/dl creatinine it would not be impossible for someone to drink enough water to reach a creatinine value of less than or equal to 5.0 mg/dl creatinine. It is more likely that specimens analyzed under the proposed procedures with apparent values in this range would result from true dilute urines (5-20 mg/dl) which have been mis-identified due to uncertainty or errors in the screening test. This could be safeguarded against by requiring a confirmation test for creatinine and specific gravity.

Substitution vs waterloading. The test combination of creatinine and specific gravity has not been evaluated for its ability to determine non-human urine ("substitution") vs ultra-dilute urine which can result from water loading and the error rate or predictive value is not known. The only studies which reported both creatinine and specific gravity after drinking water are 1.) the study from Dr. Cones's laboratory A10 which used subjects with recent histories of heroin or cocaine and marijuana use. 2.) The only study reporting creatinine and specific gravity using a normal subject was that of Coleman and Baselt 1997 B2. Subjects in these studies continued drinking water for only up to four hours compared to the much longer time intervals which occur during airline flights. The scientific studies presented by SAMSHA do not support the theoretical limit values in human urine as they contain one report of human urine with creatinine less than 1.7 mg/dl (Kern and Meislin 1984 C2) which reported a urine creatinine of 1.0 mg/dl with a specific gravity of 1.003 and a osmolality of 106 mOsm/kg. The cited studies also report specific gravity values less than 1.001 in human urine after water loading (Cone 1998 A10; Homer and Born 1993 B5, Nickman et al 1968 C22, Frizzel et al 1986 C20, Stauton and Van Allen 1967 C15 and Rinard 1989 C17).

Specific gravity to confirm creatinine screen. SAMSHA and DOT apparently believe that requiring both a creatinine less than or equal to 5.0 **and** a specific gravity of less than or equal to 1.001 constitutes a confirmation of the low creatinine value. This might be true if the specific gravity is actually confirmed by measuring specific gravity or relative density with a hydrometer (urinometer) which has been calibrated for urine and corrected for temperature deviation from the calibration temperature (Tietz 1986) or by weighing accurately measured volumes of water and urine, rather than estimated by an indirect screening method such as colorimetry, refractometry or conversion of osmolality measurements. However, the paper by Vieweg et al 1985 C8 found a variable correlation between specific gravity and creatinine in individual patients of from 0.618 to 0.935. Dr. Needleman states in his reply to commentary on his study that the study "was not directly concerned with measurement of the specific gravity of urine and the implication that measurement might have on interpreting the drug analysis results" (Needleman 1993). This would suggest that specific gravity is neither a reliable confirmation of the creatinine level nor a suitably independent measure of urine diluteness to meet forensic standards of corroboration of evidence of substitution. To meet forensic standards both creatinine and specific gravity should be confirmed as well as screened for and an independent measure of urine diluteness such as sodium, potassium, urea, or pH and human DNA or other maker of human urine should be used in forensic testing.

Osmolality. Most of the studies cited in the SAMSHA 2/14/2000 Update measured osmolality. Osmolality, which is the total amount of dissolved solids in a liquid, can not be simply converted to specific gravity, which is the density of a liquid relative to that of water as 1.000 (Tietz 1986). The relationship between specific gravity and osmolality in urine is particularly weak and deviates from the conversion based on sodium chloride solutions at the very low and very high ends of the scale as shown in the Figures 33-11 A and B (Tietz 1986, page 1556). For example, in Figure 33-11A, the specific gravity dropped below the sodium chloride equivalence line while osmolality remained at 100 mOs in urine from healthy medical students while in Figure 33-11B at the low end the osmolality changed from 100 to 300 for specimens from patients on the renal service with the same apparent specific gravity. Deviations from the equivalence line measured on sodium chloride solutions at the high values of specific gravity were even more extreme for both the specimens from renal service patients and those from healthy medical students. Several of the studies cited by the SAMSHA 2/14/00 Update show that specific gravity and osmolality change in different directions after water loading (Cronin 1987 C1. Rinard 1989 C17 and Saito 1999 C25). Measurements of osmotic concentration of urine are considered more valid than specific gravity measurements. Consequently measurement of the urine osmolality. especially as part of a concentration test, is preferred (Tietz 1986). This is reflected in the measurement of osmolality rather than specific gravity in the preponderance of the cited studies (26 of 45 studies).

The proposed changes appear to pre-date the compilation of scientific studies on dilute and ultra-dilute urine and are not supported by those studies. From the submitted literature references it appears that the addition of osmolality to the dilution testing regimen might improve the accuracy of the test interpretation. The literature references also suggest that urea, electrolyes (Na, K, Cl, HCO3) and urine color might be useful in determining urine dilution but that they do not have sufficient predictive value for diagnosis (Musch et al 1995 C9). The best test for substitution is to measure the temperature of the collected specimen within a few minutes of collection using a temperature strip attached to the collection cup. This is currently being done in all DOT collections.

Conclusions

Any criteria established for dilute or ultra-dilute specimens should be derived from evidence-based meta-studies using proper statistical methods for combination of the many literature citations of urine analytes and properties. A meta-study would be able to estimate the predictive value of various tests or combinations of tests. This meta-study should be published in a peer-reviewed journal. Commercial tests used for dilution and adulteration testing should be demonstrated to differentiate between normal and substituted or adulterated specimens and the error rate (diagnostic sensitivity, diagnostic specificity and predictive value) published. The Proposed Rules for 49 CFR Part 40 should require that any specimen validation testing be composed of initial screening tests followed by confirmation tests based on a different chemical or physical property of the analyte or property of the specimen with analysis of a split specimen at an independent laboratory for confirmation of any results certified as positive for adulterants or failing to meet any other requirement.

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Appendex I. Suggested Alterations in the Proposed Changes

1.) Re: Section 40.3 page 69097

Confirmation (or confirmatory) test should be defined for validation testing, specifically for creatinine, specific gravity, pH and nitrites and generally for other adulterants.

Screening test (or initial test) should be defined for validation testing specifically for creatinine, specific gravity, pH and nitrites and generally for other adulterants.

"Substituted" specimen. The word substituted is pejorative, "ultra-dilute" would be better as the laboratory can only determine the presence of analytes or the characteristics and properties of submitted specimens not the intent of the donor or legal, ethical or medical cause of those properties of the submitted specimen.

2.) Re: Section 40.67 (a) page 69103

Add item (3) If drug test result was ultra-dilute.

3.) Re: Section 40.91 page 69106

40.91 (a) last sentence should read "if the urine was dilute or if the specimen was ultra-dilute" since the laboratory can only determine the presence of analytes or the characteristics and properties of submitted specimens not the intent of the donor.

4.) Re: Section 40.93 page 69106

40.93 (c) For ultra-dilute specimens at a minimum creatinine must be measured on two separate aliquots from the primary specimen by at least two methods based on different chemical or physical properties of the analyte, at least one of which must be a quantitative procedure. At a minimum, specific gravity or osmolality must be measured on two different aliquots by different methods, one of which directly measures specific gravity (such as a urine-calibrated hydrometer) or osmolality.

40.93 (d) for adulterated specimens, concerning pH and nitrites, at a minimum two procedures based on different chemical or physical properties of the analyte must be performed on two different aliquots of the primary specimen. One procedure must be qualitative and utilize the specified cutoff, 3.0 or 11.0 for pH (this will probably require the use of a pH meter with glass electrode). For nitrites one method must be quantitative, both methods must employ the cutoff of 500 ug/ml and the confirmation test method must be based on a chromatographic procedure.

5.) 40.93 (e) for adulterant analytes without a specified cutoff (e.g. glutaraldehyde, bleach, soap) two methods based on different chemical or physical properties of the analyte must be performed on two separate aliquots of the primary specimen.

6.) Add rule that when the primary sample test results are certified and verified by the MRO as ultra-dilute or adulterated, the laboratory must immediately send

the split sample to a qualified independent laboratory (specified by agreement or contract in advance) for reconfirmation of the adulterant or creatinine, specific gravity and osmolality using a quantitative confirmation test.

Correct two mis-prints of $\leq$ on page 69106 last column second paragraph and fifth paragraph: $\leq$ 1.020 should read $\geq$ 1.020 and $\leq$ 11 should read $\geq$ 11.

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The International Association of Forensic Toxicologists: Secretary 1990 - 1996; Editor, TIAFT Bulletin, 1990-1996; United States Regional Representative, 1996-present, Chair 1998 Annual Meeting, Albuquerque, New Mexico.

National Committee for Clinical Laboratory Standards; Chair, Toxicology Area Committee 1990-1994; Chair, Subcommittee on Immunoassays in Toxicology; Advisor, Subcommittee on Urine Drug Analysis.

Society of Forensic Toxicologists; Past President, 1996; President, 1995; Vice-President, 1994; Secretary, 1992-1993; Board of Directors, 1990-1991, Guest Editor SOFT Special Edition, *Journal of Analytical Toxicology* 1990.

California Association of Toxicologists: Recording Secretary 1982-84, Vice President 1984-85; President, 1985-86; Immediate Past President, 1986-87, Member-at-Large, 1988-91.

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Journal of Analytical Toxicology, Editorial Advisory Board, 1991-present.
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Editor, TIAFT Bulletin, 1990-1996.
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FELLOWSHIPS, AWARDS

1986-87	Fulbright Grant in Aid, US-UK Fulbright Commission
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1984	General Section Award in Toxicology, American Academy of Forensic Sciences
1978-79	Swedish Medical Research Council, Fogharty International Post-Doctoral Fellowship
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USA CORNER

"Is Dilute Urine A Crime?"

The View from USA, Vina Spiehler, Ph.D., DABFT

Yes, in the USA, since the new Federal regulations on reporting urine specimens with creatinine less than 20 mg/dl as "Dilute" and reporting urine specimens with 5 mg/dl or less as "Substituted". A number of workers have been dismissed from their jobs and consequently lost their medical insurance at the very time when increased thirst, frequent urination, dilute urine and family history of endocrine disease indicate the need for medical investigation. Since the United States has no national health program, loss of a job means loss of medical benefits. If a person is diagnosed with a major medical problem while unemployed and uninsured, this "pre-existing" condition disqualifies them from coverage by the private medical insurance programs in the USA. From the point of view of the Unions, the new regulations discriminate against people who may need medical diagnosis and intervention.

From the point of view of the Laboratories, the Federal guidelines for reporting "Dilute Urine" do identify urine specimens which are not as concentrated as the usual urine from an individual or a population and therefore that may not be as good an indicator of recent (2-3 day) drug use using the current SAMSHA cutoffs. The scientific basis for normalizing urine drug concentrations to urine creatinine values is well established. Recent reports suggest that normalizing the urine drug cutoff concentrations to creatinine values might be useful as well.

Introduction

Creatinine is a metabolite of creatine that is not reused in the body and is thus a waste product of creatine. Formation of creatinine is reasonably constant and about 2% of the whole body creatine is metabolized to creatinine every 24 hours. Consequently creatinine formation is directly proportional to total muscle mass and roughly proportional to body weight. Increased protein intake can result in increases in creatinine production of the order of 10%[1]. Intra-individual variability in renal excretion of creatinine can be assigned to the amount of dietary creatine and creatinine ingested in meat[2]. This variability may account for the 15- 20% between day variation in calculated creatinine clearance for a given individual.

Creatinine excretion is less in women than in men and decreases in the middle of the menstrual cycle[3]. Creatine excretion decreases with age. Creatinine clearance is increased by acute infection, injury, rigorous exercise and diets high in protein, creatine and creatinine. The measurement of spot urine creatinine as a measure of specimen validation is biased against women, vegetarians, elderly, people of low muscle mass and those who are drinking water as recommended for weight loss, as these people may have normal spot urine creatinine levels of less than 20 mg/dl more frequently than the general population.

24 hour creatinine clearance is a measure of kidney function. Spot or random urine specimen creatinine is a measure of the concentration or dilution of the urine being output by the kidney. It is a function of creatinine clearance and water intake.

Effect of Drinking Water on Creatinine Levels in Urine

Lafolie et al 1991[4] reported that when 23 healthy Swedish staff volunteers drank 0.5 l of water during 15 min, they produced spot urine concentrations of 0.7- 22.7 mmol/l (8 - 256 mg/dl) creatinine and 95% of the specimens were less than 3.8 mmol/l (43 mg/dl) for up to 5 hours later. When they drank 1.0 l of water during 15 min, they produced spot urine concentrations of < 0.7 mmol/l (<7.9 mg/dl) creatinine in 95% of specimens for up to 5 hours. Spot urines from the volunteers before the test ranged from 0.1 to 31.9 mmol/l (1.13 to 360 mg/dl).

Needleman et al 1992[5] reported that Navy volunteers ingesting 125 ml (4.4 oz) of water hourly dropped from an average creatinine value of 170 mg/dl to 100 mg/dl in 4 to 7 hours. Volunteers ingesting 250 ml (8.8 oz) water hourly dropped from the mean of 170 mg/dl to <50 mg/dl in 6-7 hours. In individual charts shown in the paper, individual spot results appear to drop below 10 mg/dl. Needleman established a "normal" range of 30 - 300 mg/dl (97.1% of values) from 350 single collection random urine specimens from Navy recruits. Three specimens had creatinine < 10 mg/dl and ten were < 20 mg/dl.

Cone et al 1998[6] reported that seven healthy volunteers who drank only 12 oz of water produced urine specimens with creatinine levels of 19 to 157 mg/dl. When the seven volunteers drank one gallon of water (64 oz) (one quart per hour from 8 am to 11 am) they produced urine with creatinine levels less than 20 mg/dl (range 4-20 mg/dl) and specific gravity less than 1.003 beginning within the first hour of drinking and lasting for up to 4-6 hours. Before the study the seven produced five urine specimens with creatinine values less than 20 mg/dl in a total of 335 specimens (1.4%).

Standard nutritional advice is that adults should drink 8 x 12 oz glasses or 96 oz of water a day. If a person drank half of this (48 oz) before breakfast or lunch to

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reduce appetite, as recommended by Dr. Gullo[7], then they would be expected to produce dilute urine at random tests conducted during the day.

ANALYSIS OF CREATININE

Analysis of creatinine is usually done by spectrophotometric methods based on the Jaffe reaction. This is relatively non-specific. A color product is also formed with protein, glucose, ascorbic acid, cephalosporins, etc. These compounds usually cause an overestimate of true serum creatinine of 0.2 to 0.4 mg/dl and have very little effect on urine creatinine results unless a person is taking an antibiotic. Enzymatic assays using creatinine iminohydrolase and creatinine amidohydrolase are available but suffer from an ammonia interference. The definitive method for creatinine is isotope dilution mass spectrometry. A candidate reference method for creatinine uses HPLC with UV detection.

NORMALIZATION OF URINE DRUG CONCENTRATIONS TO URINE CREATININE

Manno[8] recommended normalization of cannabinoid levels to urine creatinine for comparison to previous results. More recently Huestis and Cone[9] have confirmed the usefulness of the THCA/creatinine ratio in determining whether marijuana exposure has re-occurred or if the presence of THCA in urine is due to continued clearance from the body. Cone[10] also reported on normalization of cocaine urine testing results to urine creatinine.

DRUG POSITIVE RATE IN DILUTE SPECIMENS

Lafolie et al 1991[4] concentrated by evaporation ten dilute urine specimens from known drug users which had tested negative by immunoassay and found that the concentrated urine was positive in five of the ten cases. They recommended concentrating specimens with a creatinine value less than 4.0 mmol/l.

Cone et al 1998[6] found that in three of seven volunteers who were given 40 mg cocaine or smoked a 3.58% marijuana cigarette, after drinking one quart to one gallon of water, the day after drug dosing, the dilute specimens with less than 20 mg/dl creatinine and with less than 1.003 specific gravity also resulted in false negative immunoassay screening tests using the current SAMSHA cutoff values for THCA but not for benzoylecgonine.

Sample[11] reported to the NLCP Inspectors meeting in October 1998 that of 615,389 urine samples received at SmithKline Beecham in May-June 1998, 5.5% had less than 20 mg/dl creatinine, 1.1% had less than 10 mg/dl creatinine and 0.1% has a creatinine of less than 6 mg/dL. 2.6% were reported as dilute. The low creatinine samples had 2-3 times the positive rate as the urine specimens overall.

It is clear that the use of absolute cutoff concentration values ignores the effect of urine concentration on the sensitivity of the tests. It seems prudent to follow LaFolie's recommendations[4] to concentrate the specimens or alternatively to normalize the cutoff concentrations in the same manner that urine drug concentrations are normalized.

REPORTING CRITERIA AND LOSS OF EMPLOYMENT

In the USA Federal National Laboratory Certification Program, laboratories are required to measure creatinine and specific gravity of urine specimens. A sample will be reported as "Dilute" if the creatinine is less than 20 mg/dl and the specific gravity is less than 1.003. Cone reported that this occurs normally in 1-2% of urine specimens (5 out of 355 specimens or 1.49%) both inter-individuals and intra-individual[6]. In the SAMSHA NLCP program a sample will be reported as "Substituted" if the creatinine concentration is <5 mg/dl and the specific gravity is <1.001 or > 1.020.

The report of a "Dilute" urine has resulted in job loss for the urine donor. More often it is cause for requiring regular urine re-testing after collection under direct observation. A "Substituted" urine specimen is grounds for dismissal of the worker from his/her job in most workplace testing programs. Following LaFolie's recommendations[4], it would fairer for the laboratory to concentrate urines with low creatinine concentrations. Or administratively, the drug testing program could use creatinine normalized cutoffs. Thus a correction for deliberate or accidental urine dilution would be achieved without penalizing persons for their physiological or medical state.

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SOCIETY OF HAIR TESTING

CONSENSUS OF THE SOCIETY OF HAIR TESTING ON HAIR TESTING FOR DOPING AGENTS

From June 14 to 16, 1999 about one hundred scientists met in Martigny (Switzerland) for the 2nd International meeting of the Society of Hair Testing.

The Society of Hair Testing was established in December 1995, in Strasbourg (France). Since the beginning, Dr Hans Sachs (Munich, Germany) has been the President of this association of 130 members.

Among the topics that were discussed (analytical procedures, pharmacology, racial bias, interpretation of the results ...), Christian Staub (meeting host) proposed to discuss the applications of hair testing in doping control.

Scientific presentations, posters and discussion sessions made significant contributions to the science of hair analysis for doping agents and attendees were encouraged to voice their agreement to the proposed statement or to suggest modifications. Point by point the statements were then summarised and a consensus was obtained.

1. Hair analysis can essentially contribute to doping analysis in special cases, in addition to urine.
2. Hair specimens are not suitable for general routine control.
3. In case of positive urine results, the negative hair result cannot exclude the administration of the detected drug and cannot overrule the positive urine result.
4. In case of negative urine result, the positive hair result demonstrates drug exposure during the period prior to sample collection.
5. Before using hair analysis for doping control, sample collection and analytical methods have to be harmonised with respect to the sophisticated requirements already valid for urine.
6. The Society feels responsible to support efforts that lead to this harmonisation.
7. This statement was adopted on June 16, 1999 by the Society of Hair Testing.

Pascal Kintz,
Secretary of the Society

PROGRESS IN FORENSIC SCIENCE

P.A. Toseland, Burgess Hill, Sussex.

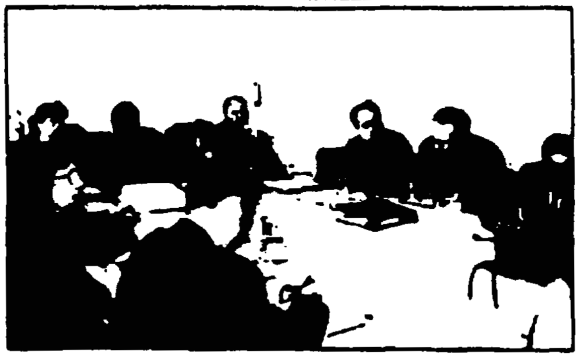
Toxicological investigation of death by poisoning, requires (a) a knowledge of the case history and suitable biological specimens, along with a comprehensive history, (b) the analysis itself and (c) interpretation of the analytical findings.

Concern about the potentially adverse effects of substance abuse to the individual, his/her workplace and society has resulted in the development of large scale, commercial urine analysis for the detection of controlled or illicit substances. In my view, post mortem toxicological investigation and specific illicit drug testing in urine (not involving death) should be conducted in separate laboratories. If the two came together and a generation of toxicologists grew up in the belief that compounds of toxicological interest - or their metabolites - will always be found in the urine, then forensic toxicology would be the poorer.

The considerable increase in analytical detection limits has outstripped our ability to interpret the results. In fact, over the last twenty years, we have come to appreciate that post mortem blood

VIEW FROM EUROPE

European Society for Workplace Drug Testing



The 'core' group of the European Society for Workplace Drug Testing met in Dublin on November 19, 1999. Twelve countries were represented by 13 people.

The website of the society will be moved from www.cbft.unipd.it/ewdts to www.ewdts.org. More information on the situation of workplace drug testing in different European countries will be added when it becomes available. It has become clear that it is not easy to find information on workplace drug testing in some countries, but partial information on each country should be online by early February 2000.

The preparations for the congress in Padua are well under way. The deadline for abstracts is February 28, 2000 and the scientific committee has already invited some speakers. In addition, the guidelines will be presented. More information can be found at: http://www.cbft.unipd.it/ewdts/. Scientists from many countries inside and outside of the EU have expressed interest in the meeting. Special efforts will be undertaken to increase the attendance by non-toxicologists.

The United Kingdom Laboratory Guidelines for Legally Defensible Workplace Drug Testing were discussed at length. The group agreed on the high quality of these guidelines. With a few minor modifications, the UK guidelines could be accepted by the EWDTS. It was decided to get into contact with the UK group in order to see if an agreement is possible in order to have only one set of guidelines.

A first draft of the bylaws of the society was agreed upon. In the interim, three people will form the interim committee: Per Bjorklov (Sweden), Anya Pierce (Ireland) and Alain Verstraete (Belgium). During the congress in Padova the members will elect a new board. It was agreed that the membership fee would be 25 Euro. However, anyone who attends the Padua Scientific Meeting will get one-year free membership after completing the application for membership form.

Dr. Alain Verstraete

VIEW FROM USA

Must Workplace Tests Meet Forensic Standards?

Vina Spiehler, Ph.D., DABFT

A mature engineer with 15 years service with his company and no history of alcohol or drug abuse was summarily dismissed from his job for "tampering" when a dipstick test for nitrites was positive on his otherwise negative urine specimen. A popular airline stewardess, a petite vegetarian lady of Asian background, was fired for "substituting" her urine specimen after her strenuous efforts at hydration during and after a trans-Pacific flight resulted in a creatinine and specific gravity reading below program cutoffs. For employees subject to urine drug screening sometimes the penalties for abnormal urine characteristics are more severe than those for the presence of drugs in their urine. Therefore the chemical test results, which are used to invoke these penalties, must meet stricter forensic standards and safeguards than those for drug tests.

Changes in USA Programs

In the past the tests for adulteration and dilution have not been subject to the same requirements of validation, quality control, confirmation by an independent procedure and the right of the donor to challenge the results by re-testing a split sample as the drug results. In fact, at times the tests have been unconfirmed simple colormetric or dipstick tests without quality control which were developed and cleared by FDA for diagnostic purposes, not for detection of adulterants. To ensure that all tests used for forensic purposes meet the highest standards, the United States federal government departments responsible for mandated employee testing (Department of Transportation) and laboratory certification (SAMHSA-NLCP) have issued revised program guidelines and are considering rewriting the regulations for tests for pH, creatinine, specific gravity, nitrites and adulterants.

In July 1999 SAMHSA issued a memo (PD37)[1] requiring that creatinine and specific gravity of urine specimens must be measured by quantitative procedures which are accurate and reproducible at cutoffs of 5 mg/dl and 20 mg/dl and 1.001 and 1.020 respectively. Controls above and below the cutoffs employed must be run with each batch. The limit of detection (LOD), limit of quantitation (LOQ) and linearity for the methods employed must be experimentally determined and the procedures used to characterize and validate these tests must be documented in the laboratory's SOP.

PD 37 also requires that measurements of pH and nitrites be performed by, at a minimum, two procedures, of which one procedure must be quantitative and utilize the specified cutoff. The specified cutoff for pH is less than or equal to pH 3 or greater than or equal to pH 11. The procedures must be performed on separate aliquots. For adulterant analytes without specific cutoffs such as a glutaraldehyde, bleach, surfactant, etc at least one procedure must be performed on two separate aliquots.

Any test for which the cutoff uses the criteria of "equal to or less than" or "equal to or greater than" must be carried out to a decimal place beyond that of the cutoff, since truncating would change the result from acceptable to unacceptable (e.g. truncating a pH reading of 3.2 to 3 or a creatinine of 5.4 mg/dl to 5 mg/dl). This does not apply to specific gravity, which need only be measured to the third decimal place (< 1.001), but does require that refractometry be used (and laboratory technicians be trained to use it properly) since the directive does not credit spectrophotometric and paper/stick procedures with the sensitivity to accurately discriminate in that range.

Forensic Standards

Although the rules of evidence in different regions vary, there is a general consensus that evidence presented for court must be corroborated by performing more than one test and that the different test procedures should be based on different chemical or physical properties of the analyte[3]. Also, the confirmation test should offer a higher degree of specificity for the analyte in question than the screening test[3]. Therefore a second immunoassay can not confirm an immunoassay screen. Repeating a test is not a confirmation. Confirmation tests should be performed on an independent aliquot of the original specimen. This should ensure that the final confirmed result has a predictive value (probability of being correct) sufficient to allow the toxicologists to interpret the result with scientific certainty[3].

The revised directives from SAMSHA (PD #37) have begun to institute these principles in tests for dilution and adulteration of urine specimens. Separate aliquots are required for corroborative tests. However the requirement that the corroborative test be based on a different chemical or physical property of the analyte has not yet been recognized. Therefore a spectrophotometric procedure using the Griess test[4,5] for nitrites might be "confirmed" by a dipstick test using the same chemical reaction[6] under these regulations.

A second principle of forensic testing is performance of quality control testing. SAMSHA has always required that urine matrix control samples below and above the cutoff values as well as calibration standards be run in every batch for drug testing. Controls at concentrations below and above the cutoff are also now required for adulteration and dilution testing as well.

Human Rights and Scientific Certainty

When a drug or drug metabolite is detected in an employee's specimen, they may request that the urine or urine split be re-tested by another laboratory SAMSHA PD 35[7] specified that an employee whose urine specimen characteristics falls outside the above cutoffs may not request a re-test of the split or original specimens by a second laboratory.

The rights of the accused employee to challenge the test results by having the split urine specimen re-tested by an independent laboratory is a human rights question not a scientific question. When the regulations do not permit such challenges, the ethical burden on the scientist to be certain of his results is increased. Whenever test results are used for legal or forensic purposes that result in judgment and penalties for individuals, the testing must meet the highest standards and result in a probability or scientific certainty beyond a reasonable doubt. For many jurisdictions this means a probability of greater than 95%. By combining an immunoassay screen and a GC/MS SIM assay using two ion ratios and deuterated internal standards, the predictive value of a confirmed positive drug result is greater than 99.9%[3]. If the probability of a drug true positive should be better than 99.9%, then perhaps the probability of an adulteration or dilution result should be greater than 99.99%. This will require chromatographic confirmation of spectrophotometric or colorometric detection assays for adulterants. The scientific community is responding to the challenge of confirmation of urine adulteration, contamination and substitution. For example, Singh *et al* reported an ion chromatographic test for nitrite[8] which is more specific than the Griess reaction commonly used in dipstick and liquid reagent tests for screening for nitrites and is based on a different physical property of the analyte.

Of course an alternative to the growing problem of urine adulteration might be to test biological samples such as hair, sweat or saliva which are not subject to adulteration and dilution or whose sampling can be directly observed. And whose tests can be performed on-site.

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The Urine Specimen Defined as Substituted

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Substituted Urine Definition

- A specimen is defined to be ***substituted*** (*i.e.*, the specimen does not exhibit the clinical signs or characteristics associated with normal human urine) if the creatinine concentration is ≤ 5 mg/dL <u>and</u> the specific gravity is ≤ 1.001 or ≥ 1.020.

PD 35; 11/28/98

Specimen Validity Testing

- Specimen validity testing shall be conducted utilizing the following criteria:
  - For substituted specimens, at a minimum, creatinine must be measured by at least one quantitative procedure on two different aliquots, both using the specified cutoff of 5 mg/dL.
  - At a minimum, specific gravity must be performed on one of these aliquots utilizing the specified cutoffs of 1.001 or 1.020.

PD 37; 7/28/99

Issue #5 – Significant Figures

- Creatinine values should contain one significant decimal place more than that stated in the decision point.
- Creatinine values ≤ 5 mg/dL may <u>not</u> be truncated.
  - *i.e.* 5.4 mg/dL is not equivalent to 5 mg/dL
  - Value must read 5.0 or less

PD 37; 7/28/99

Issue #5 – Significant Figures

- Specific gravity must be measured to the 3rd decimal place.
  - *i.e.*, 1.001
  - Refractometry is required

PD 37; 7/28/99

Issue #6 – Quality Control

- Each assay must have at least one control in the "acceptable" range and one control in the "unacceptable" range for each batch of tests.
- Controls should be prepared in an appropriate urine matrix and validated prior to use.

PD 37; 7/28/99

Analytical Considerations

- Creatinine
  - Methods: Jaffé, enzymatic
  - CAP CV 15%, typically < 10%
- Specific gravity
  - Methods: refractometer, ionic strength

Analytical Considerations

- Method validation
  - SOP
  - Controls above and below the decision values
- Forensic principles
  - Two protocols based on different analytical principles
  - Two aliquots from original specimen

Physiological Considerations

- The case for ≤ 5 mg/dL creatinine and ≤ 1.001 specific gravity
  - Theoretical values
  - Normal values
  - Random clinical studies
  - Medical conditions resulting in super hydration
  - Specific water loading studies

Theoretical Limit Values

- Creatinine: 1.7 mg/dL
- Specific gravity: 1.001
- Renal free water excretion capacity of kidneys is 20 mL/min which is equal to 29 L/d
- Typical urine production is 0.6 - 1.8 L/d

Random Reference Ranges

Creatinine	18 - 200 mg/dL
Osmolality	50 - 1400 mOsm/kg
pH	4.5 - 8.0
Specific Gravity	1.002 - 1.030

Random Clinical Studies Data

Random Clinical Studies Summary

- No exception to substituted criteria seen in medical populations
- Several exceptions to substitution criteria seen in drug test populations

Substituted Urine Statistics

- Regulated specimens submitted to Quest Diagnostics, Atlanta, during January and February 1999
- 12 of 58,475 (0.02%) classified as substituted

Medical Conditions

- Polydipsia
  - Frequent drinking of fluids
- Psychogenic polydipsia
  - Excessive fluid consumption resulting from a disorder in personality, without a demonstrable organic lesion

Medical Conditions

- Water intoxication
  - Severe overhydration which may result in convulsions and death due to uncorrected hyponatremia and cerebral edema.
- Diabetes insipidus
  - The chronic excretion of very large amounts of pale urine of low specific gravity, accompanied by extreme thirst, resulting from inadequate amounts of pituitary antidiuretic hormone

Medical Conditions

- Nephrogenic diabetes
  - The chronic excretion of very large amounts of pale urine of low specific gravity resulting from the inability of the kidneys to respond to antidiuretic hormone (ADH)
- Iatrogenic diabetes
  - Diabetes induced by an unfavorable response to a therapeutic intervention

Medical Conditions Data

Medical Conditions Summary

- Data not complete on paired creatinine/specific gravity specimens
- No substituted criteria met where paired data exists

Water Loading Data

Water Loading Summary

- Data not complete on paired creatinine/specific gravity specimens
- No substituted criteria met where paired data exists

Conclusions

- The review of the scientific literature including random clinical studies, medical conditions resulting in severe overhydration and a group of water loading studies suggests that the criteria of creatinine ≤ 5.0 mg/dL and a specific gravity ≤ 1.001 presents a condition in a urine specimen which is not consistent with normal human urine.

Conclusions

- Current hydration studies are limited.
- Additional controlled hydration studies would be valuable to expand our current base of knowledge.

Acknowledgement

- Consultants to the Division of Workplace Programs, SAMHSA on this project:
- Literature review and data analyses performed by Janine Denis Cook, Ph.D., DABCC, University of Maryland, Baltimore/SOM/DMRT, and
- Literature review performed by Ted Piatkowski, M.S., Quest Diagnostics Inc., Baltimore, MD

The Urine Specimen Defined as Substituted

Random Clinical Studies

Number of Subjects/	Creatinine Range, mg/dL	SG Range	Population	Notes	References
14	≥ 10	1.002 – 1.024	Medical		A1
350	172 +/- 81		Medical	All creatinines > 10 mg/dL	A1
50	1.1 - 29	1.001 – 1.084	Drug	No paired data	A2
176	1.1 - 361		Drug		A3
10	183 ± 85		Medical		A4
9 subjects / 1206 samples	18 - 532	1.002 – 1.036	Drug		A5
1601		1.000 – 1.055 (binned data)	Drug	0.37% in 1.000 – 1.005 data bin	A6
423		1.001 – 1.040	Drug	10% in 1.001 – 1.010 data bin	A7
37	20 - 477		Medical		A8
67	18 - 200		Medical		A9
7	7 - 318	1.001 – 1.029	Drug		A10

The Urine Specimen Defined as Substituted

Medical Conditions Studies

Number of Subjects	Condition	Creatinine, mg/dL	SG	Osmolality, mOsm/kg	Notes	References
11	Psychogenic Polydipsia		1.002 – 1.024	45 - 530		C1
1	Diabetes Insipidis		1.003	106	12 – 15 L/d	C2
1	Diabetes Insipidis		1.007	296	8.5 L/d	C2
1	Psychogenic Polydipsia			84	> 6 L in "few" h	C3
1	Water Intoxication			237	6 L/d	C4
1	Water Intoxication			142	19 L/6 h	C5
1	Water Intoxication			78	1.44 L ingestion Seizures, coma	C6
1	Diabetes Insipidis	13	1.005	54	4 – 6 L/d	C7
10	Psychogenic Polydipsia	4 - 185	1.000 – 1.017		No paired data	C8
3	Polydipsia			144 +/- 23		C9
1	Iatrogenic Polydipsia			313	15 – 18 L/d	C10
14	Polydipsia			122 +/- 66 112 +/- 57		C11
10	Polydipsia			> 50	20 ml/kg water load in 10 min	C12

The Urine Specimen Defined as Substituted

Water Loading Studies

Number of Subjects	Dose	Creatinine Range, mg/dL	SG Range	Pairs	Notes	References
6	4 mL/kg over 10 h		1.012 ± 0.002	No creatinine data	Osmolality: 295 +/- 69 mOsm/kg	B1
1	1.2 L/1 h 1.1 L/30 min 1.4 L/75 min	32 - 157	1.004 – 1.014	Lowest pair: 32 creatinine 1.005 SG	Lowest creatinine: 32 mg/dL	B2
6	1.0 – 2.0 L/4 h	>/= 30	1.003 -- 1.010			B3
7	3.8 – 4.2 L/4 h	4 - 266	1.000 – 1.030	Lowest pairs: (4 : 1.003) (5 : 1.003)	SG ≤ 1.001 paired with 8 – 12 mg/dL creatinines	B4
2	3.4 - 3.8 L/4 h		1.000	No creatinine data	Only value claimed	B5
23	0.5 L/15 min	8 - 257			Osmolality: 69 – 1075 mOsm/kg	B6
23	1.0 L/15 min	7 - 257			Osmolality: 45 – 996 mOsm/kg	B6
20	0.8, 1.0 and 1.5 L/BSA (m^2)/d		1.025 (0.003) (0.8 L/BSA) 1.022(0.005) (1.0 L/BSA) 1.015(1.010) (1.2 L/BSA)			B7
8	20 mL/kg				Osmolality: 32 – 95 mOsm/kg	B8
9	5.6 ± 1.8 L/21 h		1.005 – 1.025		Osmolality: 200 – 850 mOsm/kg	B9

References for The Urine Specimen Defined as Substituted

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BEFORE THE
DEPARTMENT OF TRANSPORTATION

Federal Aviation Administration **In the Matter of:** **Antidrug And Alcohol Misuse Prevention Programs For Personnel Engaged In Specified Aviation Activities** **Notice No. 00-14**	**Docket No. FAA-2000-8431**
Coast Guard **In the Matter of:** **Chemical Testing**	**Docket No. USCG-2000-7759**
Research and Special Programs Administration **In the Matter of:** **Drug And Alcohol Testing For Pipeline Facility Employees** **Notice No. 1**	**Docket No. RSPA-00-8417**
Federal Railroad Administration **In the Matter of:** **Control Of Alcohol And Drug Use: Proposed Changes To Conform With New DOT Transportation Workplace Testing Procedures** **Notice No. 48**	**Docket No. FRA-RSOR-6**

Federal Motor Carrier Safety Administration)
)
In the Matter of:)
) Docket No. FMCSA-2000-8456
Controlled Substances And Alcohol Use)
And Testing)
)

Federal Transit Administration)
)
In the Matter of:)
) Docket No. FTA-2000-8513
Prevention Of Alcohol Misuse and)
Prohibited Drug Use in Transit Operations)
)

COMMENTS OF
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AND
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COMMENTS OF
THE AIR LINE PILOTS ASSOCIATION AND
THE TRANSPORTATION TRADES DEPARTMENT
OF THE AFL-CIO

Introduction and Summary

The Air Line Pilots Association ("ALPA") is the principal labor union representing the nation's commercial pilots. It represents more than 66,000 pilots at 47 airlines in the United States and Canada. The Transportation Trades Department of the AFL-CIO ("TTD") is an organization of the AFL-CIO comprised of 33 unions that represent employees in the transportation industries.[1] ALPA submits these comments on its own behalf and on behalf of TTD in response to the above-captioned Notice of Proposed Rulemaking ("NPRM").

ALPA and TTD maintain their opposition to mandatory "validity" testing in the manner in which DOT is seeking to implement it. We remain concerned that validity testing lacks fundamental safeguards, fails to meet acceptable scientific standards and continues to present an unacceptable risk to innocent employees.

Recent history has shown that innocent workers have been falsely reported to have adulterated or substituted their urine samples, and have been terminated from their jobs as a result. The severe consequences to an individual accused of tampering with his or her specimen demands that any such testing be in accordance with the highest standards of forensic science and due process.

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[1] The unions represented by TTD are listed in the attachment to these Comments.

While we appreciate that DOT incorporated some of our suggestions in the final version of Part 40, many of our basic concerns remain unresolved. We refer the Department to ALPA's Comments submitted in response to the NPRM on Part 40 (Notice OST-99-6578) and incorporate by reference the concerns stated therein. (See Attachment).

As we emphasized in our prior Comments and as has been born out by ALPA's experience after the close of the Part 40 NPRM comment period, if validity testing in accordance with the rules now in effect under Part 40 is going to be required, it is absolutely essential that employees and labor unions have access to information in the possession of employers, service agents and laboratories that can reveal laboratory and other testing, analytic and reporting errors. It is similarly vital that employees and labor unions have the right to a forum within which to present and have considered such exculpatory evidence. We strongly object to the proposed deletion of the access to information provisions in the drug and alcohol testing regulations of the FAA and other transportation sector agencies. Nor do we consider the release of information provisions in Part 40 sufficient to adequately protect employees. In our view, the failure to provide employees access to such relevant information denies them due process.

Finally, we recognize and appreciate the revisions and clarifications in FAA's drug and alcohol testing regulations that have been proposed to make them consistent with the prior changes to the airmen medical certification regulations and standards in 14 C.F.R. Part 67.

I. EMPLOYEES' REGULATORY RIGHTS TO OBTAIN INFORMATION SHOULD BE ENHANCED NOT DIMINISHED.

A. The Provisions In The Drug And Alcohol Testing Regulations Setting Forth Employers' Obligations To Provide Employees With Relevant Information Should Not Be Deleted.

Currently both drug and alcohol testing regulations have provisions that entitle employees to obtain, and require employers to provide, records relevant to charges that an employee violated the anti-drug and alcohol misuse provisions. For example, with respect to alcohol misuse, "[a] covered employee is entitled, upon written request, to obtain copies of any records pertaining to the employee's use of alcohol, including any records pertaining to his or her alcohol tests." 14 C.F.R. Appendix J to Part 121, IV.C.2. A similar provision exists in the drug testing regulations obligating an employer to release "information regarding an employee's drug testing results, evaluation, or rehabilitation" upon an employee's written request. 14 C.F.R. Appendix I to Part 121, VI.D.

The NPRM proposes to delete each of these provisions, stating that access to information is provided for under the revised Part 40. However, Part 40 does not contain similar language and is, in itself, far too limited in the information it requires to be released.

The current regulatory language that the NPRM proposes to eliminate requires a broad release of information relating to drug and alcohol use, evaluations or rehabilitation, as well as information pertaining to test results. This broad language has been valuable in providing a right of access to relevant information for employees. The language in revised Part 40 (Section 40.331) is not the same and could likely lead to disputes over the breadth of its reach. It is essential that the regulations continue to protect employees' right of access to such information.

The current regulatory language also places the burden on employers to provide such information. This is as it should be, and should remain. While we agree that MROs, laboratories and other service agents should be directly responsible under the regulations to provide information to employees, and subject to DOT sanction (or the Public Interest Exclusion) if they fail to comply with their regulatory obligations, employers should also remain responsible and accountable for ensuring that the MRO, laboratory or other contracting service agent properly fulfills its obligations under the regulations. The contractual relationship the employer has with both the MRO and the laboratory gives the employer leverage in securing timely compliance with disclosure provisions. Eliminating the employer's responsibility invites a prolonged battle for access to information between the worker and the MRO, laboratory, and other service agents. The regulatory language should be clear that the employer remains ultimately responsible for ensuring that employees are provided with such information.

B. <u>Laboratories And Other Service Agents Should Be Required To Produce Extensive Information To Affected Employees To Afford The Opportunity to Identify Gross Laboratory Errors</u>.

In the prefatory section to the issuance of the revisions to Part 40, DOT describes a "significant series of errors by one laboratory involved in validity testing" that it learned of in September 2000. 65 Fed. Reg. 79481 (Dec. 19, 2000). DOT describes some of the problems and reports that (a) caused the employer in that case to terminate its contract with that laboratory and re-hire five employees whose test results had been thrown into question by the laboratory's errors; (b) caused the laboratory director to resign; (c) caused DOT to refer issues of possible evidence tampering by the laboratory to the DOT and HHS Inspector Generals for further investigation; and (d) caused HHS to embark on a special laboratory investigation which identified further errors resulting in the cancellation of over 300 test results. Id. at 79481-2.

As DOT is aware, ALPA handled the case that uncovered these laboratory problems. It involved a Delta Air Lines pilot with 20 years of service, a previously unblemished record and no prior evidence of any drug or alcohol problems, who steadfastly maintained his innocence of any wrongdoing, but who was fired and had his pilot's certificate emergency revoked based solely on the levels of creatinine and specific gravity reported to be in his urine by LabOne. In the same time frame that this pilot was fired, several flight attendants at the same airline were also terminated for allegedly "substituting" their urine samples, also based solely on reports by LabOne.

What is significant about the pilot's case for purposes of these Comments is that the serious laboratory problems uncovered – those pertaining to the handling and analysis of the individual's sample, as well as those reflecting longstanding and widespread laboratory practices affecting many other employees' tests – were not apparent from the Custody and Control Form ("CCF") nor the "litigation" or "data package." For this reason, it is essential that the regulations make clear that employers, laboratories and other service agents are not limited to producing only the CCF and litigation or data package to employees.

In the pilot's case, it was only by obtaining additional and extensive documents and testimonial evidence through formal discovery that the problems were revealed. It is also noteworthy that the pilot's case settled after glaring laboratory misconduct came to light prior to trial, and therefore before ALPA had the opportunity to put on other extensive evidence it had gathered from voluminous laboratory documents and NLCP inspection reports, which revealed numerous, equally significant, laboratory problems.[2]

Because the pilot was a certificated employee, and because the FAA revoked his license at that time, he was entitled to the NTSB appeal procedures, including discovery, judicially ordered subpoenas, and a hearing before an administrative law judge. The ability to use these procedures and gain access to extensive laboratory documents and have them analyzed by an outside expert was outcome determinative. Without access to such information, an employee would not be able to identify significant laboratory problems of the type encountered in that case.

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[2] Although the pilot was reinstated with full backpay and benefits restored and his record cleared by his employer and the FAA, he is still harmed by the bias of some individuals who lack full knowledge of the extensive laboratory problems uncovered which were never put into evidence in any hearing. His case and that of the flight attendants at the same airline illustrates the extreme difficulty in getting reviewing officials to consider that numbers "officially" reported by a laboratory can be inaccurate and unreliable. Even in a case where gross laboratory misconduct is observed and extensive procedural errors found, overcoming that stigma can be an enormous undertaking.

It is useful to examine some of the specific information and the means by which it was obtained that led to the detection of the LabOne problems. In that case, among other things, ALPA obtained the lab's Standard Operating Procedures ("SOP") used for testing creatinine and specific gravity; instrument maintenance and corrective actions documents; all quality control data for the testing of specific gravity and creatinine during the month before and the month after the pilot's urine was tested; and National Laboratory Certification Program ("NLCP") inspection reports and critiques for the relevant period. All of this information was essential in order to identify various problems with the laboratory.

For example, the finding that a reading of "LLL" on the instrument reading specific gravity is an error message was not self evident from the litigation package nor did the laboratory personnel readily acknowledge it. Only by having access to, and obtaining, the SOP and the manufacturer's handbook for the instrument used to measure specific gravity was that crucial fact obtained.

It is also necessary to gain access to information to understand the cause or significance of an unusual reading or error message. Our experience shows that an error that might seem insignificant can indicate a far more serious problem when interpreted in conjunction with other facts and data.

In the pilot's case, information about the laboratory's calibration procedures, in conjunction with the "LLL" error message, the absence of a low specific gravity control, and the NLCP proficiency data, led an outside expert to conclude that the specific gravity instrument appeared to be under-reporting specific gravity levels during the applicable time period. Certain evidence about the manner in which laboratory personnel calibrated the specific gravity instruments raised questions about the nature of the water used to zero the specific gravity instrument. Using less than pure or less than fully deionized water to zero the instrument (set the meter to 1.000), would cause subsequent samples to read below 1.000. This error would be revealed by a low control or by an error message from the instrument.

At the time of the pilot's test, the laboratory failed to run a low control for specific gravity, and failed to take any corrective action in response to the instrument's error message generated when the pilot's specimen was tested. The NLCP external proficiency report for the applicable time period also reported a value for the low specific gravity proficiency test sample that was two standard deviations below the group mean. There was no documentation of review or of corrective action by the laboratory in response to that low value on the NLCP proficiency report.

Evidence such as this is highly probative as to whether reported test results are scientifically supportable. It is essential for employees and labor unions to have access to such information in order to protect innocent employees as well as the integrity of the testing system itself. It is also in the broader public interest to uncover a laboratory's errors and prevent faulty test results. ALPA's discovery of the LabOne problems in the pilot's case led to further investigation by HHS that uncovered additional problems at other laboratories meriting the cancellation of over 300 tests of other affected employees.

Quality control data is also pivotal evidence. Poor quality control can make testing procedures during a particular time frame scientifically unreliable and inaccurate. For example, the review of such data in the pilot's case revealed several significant problems. First, it showed that the lab was not using a required low creatinine control of less than 5.0 mg/dl (required by federal guidance, PD 37). Instead, for its "low" creatinine control, it used a control of 40 mg/dl and allowed a tolerance of error of $\pm$20% when testing its equipment with that control. That meant that if the 40 mg/dl control was tested and reported a result of 32 mg/dl, the laboratory considered it satisfactory. It also meant that if the controls were reporting results with such variance, so too could the actual results reported on employees' tests. Thus an employee whose creatinine level was actually "dilute" might have a lab reported result of "substituted."

Second, the quality control data showed that the actual performance of the creatinine controls had significantly deteriorated approximately two weeks before the pilot's specimen was tested. Records for both the high and low creatinine controls showed that in the weeks before the pilot's sample was tested, and in the days following it, both the low control and the high control showed multiple indicators of increased imprecision and reduced accuracy on the particular instrument used to test this pilot's urine sample. In the creatinine assay, repeated measurements on known quality control samples on the instrument used for the pilot's specimen revealed a day to day spread of 12 to 16 mg/dl at both low and high control levels, which was double the values obtained before and after this period (a spread of 8-9 mg/dl at the low control of 40 mg/dl, and a spread of 7-9 mg/dl at the high control of 73 mg/dl before and after this period). Such data indicate deterioration in the performance of the instrument on which the quality control specimens were tested, which in the pilot's case, was the same machine on which his test results were based. Under such circumstances, a reading of 0 creatinine could correspond to a true value of greater than 5 mg/dl.

Additionally, the evidence showed no SAMHSA designated official person was responsible for the quality assurance of creatinine or specific gravity testing. The laboratory's Quality Control coordinator was unqualified to, and did not, supervise or analyze quality control data for trends, bias, scatter, or acceptability by scientifically recognized criteria such as the Westgaard Rules. The NLCP inspection reports also showed that the laboratory had been repeatedly cited for quality control deficiencies by the SAMHSA NLCP inspectors.

Significantly, these data caused an outside expert to conclude that the precision and accuracy problems in the creatinine and specific gravity assays at LabOne in the applicable time period, as evidenced by the quality control records, would not have allowed a precise or accurate determination as to whether the specimens tested were below the substitution cut-offs (less than 5 mg/dl creatinine and less than 1.001 specific gravity) or merely dilute (less than 20 mg/dl creatinine and less than 1.003 specific gravity).

While there were many other laboratory errors identified from the documents obtained and the deposition testimony taken in the pilot's case, the above examples suffice to demonstrate how essential such data are to determining whether reported test results are truly accurate and reliable and justify ending a person's career and livelihood. In the pilot's case, glaring laboratory misconduct was also revealed which, in and of itself as DOT recognized, "undermined the credibility of the laboratory" and resulted in a settlement of the case. (65 Fed Reg. 79481). But even the egregious conduct (which included document manipulation – signature copying and backdating; high level laboratory personnel misrepresenting academic qualifications and then lying about them under oath; even an apparent attempt to destroy evidence) were not discernable from the litigation packet or the custody and control form. These were uncovered only after careful review of records and through deposition cross examination.

In sum, as ALPA's experience has shown, access to all relevant documentation is absolutely necessary to identify serious laboratory errors and faulty procedures. Such relevant evidence includes but is not limited to: laboratory quality control records, laboratory performance records on proficiency testing, results of laboratory inspections and critiques, all laboratory internal and external quality control data, instrument maintenance and corrective action documentation; instrument and software instruction manuals, as well as laboratory Standard Operating Procedures. Access to such information should be readily available for all employees subject to testing under the DOT regulations, and should not depend upon whether a particular individual has access to additional administrative or judicial procedures because he or she becomes subject to certificate action.

The pilot's access to information in the above case was in stark contrast to that of the terminated flight attendants at the same airline. Those individuals are non-certificated employees, not represented by a labor union, and had no clear avenue of recourse or ready access to discovery. Had evidence of the laboratory's serious deficiencies not been discovered in the pilot's case, the flight attendants may well have permanently lost their careers. Likewise a pilot not subject to certificate action and not covered by a collective bargaining agreement, or another type of uncertificated employee, who is fired based on a reported test result may have no due process rights, and can be similarly deprived of access to the very information necessary to exculpate him. For these reasons, we urge DOT to ensure that the regulations make clear that all employees have the right to obtain the type of information discussed above.

Moreover, oversight of the testing process by interested parties and affected employees is one of the best means of protecting and ensuring the integrity of the testing process. Since unions represent affected employees, they too should have the right under the regulations to receive the types of summary information and trend data made available to employers, MROs and DOT.

Finally, information about certified laboratories' procedures for testing employees under DOT-mandated tests, and any problems uncovered in the course of them, should be publicly available. We are extremely concerned about the DOT's resistance thus far to disclosing information about the over 300 cancelled tests. We are similarly disturbed about recent efforts by certified laboratories to limit access or disclosure of such information by requesting or attempting to insist on confidentiality agreements or protective orders. As a matter of public policy, such information should be publicly accessible to aid employees in identifying faulty testing procedures that may have caused the reporting of erroneous test results. DOT's greater interest should be in safeguarding the integrity of the testing program – not in protecting pecuniary interests of certain laboratories. The regulations should state that access to such information is required and that any attempts to shield such disclosure is not permissible.

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Dated: June 14, 2001

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The following labor organizations are members of and represented by the TTD:

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Association of Flight Attendants
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Communications Workers of America
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Professional Airways Systems Specialists
Retail, Wholesale and Department Store Union
Service Employees International Union
Sheet Metal Workers International Association
Transportation • Communications International Union
Transport Workers Union of America
United Mine Workers of America
United Steelworkers of America

March 2001

ATTACHMENT

February 14, 2000

NLCP: STATE OF THE SCIENCE - UPDATE # 1

Subject: Urine Specimen Validity Testing: Evaluation of the Scientific Data Used to Define a Urine Specimen as Substituted

Background

The Mandatory Guidelines for Federal Workplace Drug Testing Programs published in the *Federal Register* on June 9, 1994 (59 FR 29908) and the U.S. Department of Transportation (DOT) regulations (49 CFR Part 40) applicable to DOT federally regulated programs permit laboratories to conduct additional tests to determine the validity of a urine specimen. The laboratories certified under the National Laboratory Certification Program (NLCP) have reported that the number of adulterated, diluted, and substituted urine specimens has been increasing. In response, the U.S. Department of Health and Human Services (HHS) and DOT began the process, using the HHS Substance Abuse and Mental Health Services Administration's (SAMHSA) Drug Testing Advisory Board (DTAB), to develop standards for the testing and reporting of validity test results for urine specimens tested in federally regulated programs. The scientific consensus reached and guidance provided by the DTAB was issued in the form of National Laboratory Certification Program (NLCP) Program Documents (PDs). These PDs established the standards for performing and reporting tests for adulteration, dilution, and substitution if such testing is conducted on Federal and federally regulated specimens. At this time, validity testing is authorized, utilizing specific NLCP criteria, but is not mandatory for urine specimens collected under Federal employee drug testing programs.

Urine is an aqueous solution. Its major constituents are primarily electrolytes, metabolic excretory products and other substances eliminated through the kidneys. Creatinine is one such metabolic excretory product spontaneously formed from creatine in muscle. Thus, creatinine production is dependent upon muscle mass. Clinically, creatinine is used to assess renal function because it is excreted at a relatively constant rate.

Specific gravity and osmolality assess urine concentration, or the amount of substances dissolved in urine. As increasing amounts of substances are added to urine, the concentration of these dissolved substances and the density, or the weight of substances per unit volume of liquid, increases. Urinary osmolality determines the concentration of the dissolved substances in urine. Specific gravity measures the density of urine relative to the density of pure water. The greater the specific gravity and osmolality, the more concentrated the urine.

Creatinine and specific gravity are two common clinical chemistry parameters which characterize normal human urine specimens for a variety of purposes. Random urine reference ranges are routinely used to evaluate a donor's urine, especially in drug testing programs. Urine specimens are defined in PD #35 (see attachment 1) as "dilute" if the creatinine concentration is < 20 mg/dL <u>and</u> the specific gravity is < 1.003. A number of urine specimens reported "dilute" by these rules were so extremely low in their creatinine concentration and specific gravity that it raised doubt if, in fact, the specimen was human urine as excreted by the kidney. Some individuals, in an effort to conceal drug use will attempt to suborn any procedure employed to identify the presence of illegal drugs in a collected urine specimen. The need, therefore, to define urine specimens that are "substituted" (*i.e.*, not consistent with normal or dilute human urine) is paramount for an effective drug testing program.

Scientific Review and Evaluation

Before NLCP PDs were issued to provide guidance concerning urine specimen validity testing, an extensive review of the published scientific literature was performed to develop the criteria for defining a "substituted" specimen. The review encompassed relevant studies, the majority of which were done in the 1990s. An analysis of that review resulted in selecting urine creatinine ≤ 5 mg/dL <u>and</u> urine specific gravity ≤1.001 or ≥1.020 as the criteria to define a "substituted" specimen. Four different types of studies were evaluated:

1. Normal random urine reference range reports from a leading clinical diagnostic reference text
2. Clinical studies involving the analysis of random urine specimens
3. Medical conditions resulting in overhydration
4. Water loading studies

<u>Normal Random Urine Reference Ranges</u>

The clinically accepted reference ranges for normal random urine specimens are shown in Table 1. "Random" urine specimens refer to those obtained from the general population, including males and females of varying ages, ethnicities, (*i.e.*, Caucasian, African-American, Asian, Hispanic), persons of different body sizes and shapes, dietary habits, and other variables of human lifestyle.

Table 1. Normal random urine reference ranges.[1]

Analyte	Random Urine Reference Range
Creatinine	37 – 300 mg/dL (female) ; 44 – 250 mg/dL (male) *
Specific gravity	1.002 - 1.030
Osmolality	50 – 1200 mOsm/kg

*Based on a calculation from 24 hour creatinine and total urine volume reference ranges.

Random Urine Clinical Studies

Eleven different clinical studies enrolling normal subjects for either medical evaluation purposes or substance abuse related conditions that had reported creatinine and specific gravity in random urine specimens were identified in the published literature. A summary of these studies are found in Table 1 in the appendix.

In the urine specimens collected for medical evaluation purposes, there were no reports of urine specimens in which the "paired data" – specimens where both the urine creatinine and urine specific gravity were measured – showed the urine creatinine concentration was ≤ 5 mg/dL <u>and</u> the urine specific gravity was ≤1.001 or ≥1.020. In other words, all urine specimens collected for medical evaluation purposes met the biochemical criteria for excreted human urine. Regardless of the medical conditions studied, no donor urine specimen was identified where both the urine creatinine concentration <u>and</u> the urine specific gravity met the criteria for a "substituted" specimen.

Urine specimens collected from donors in the studied substance abuse populations where testing was done on known drug abusers inherently run the risk of being altered by a deliberate attempt aimed at suborning the results of the test and concealing illegal drug use. Nonetheless, no urine specimen identified in these studied substance abuse populations met the substituted urine specimen criteria where <u>both</u> the urine creatinine concentration was ≤ 5 mg/dL <u>and</u> the urine specific gravity was ≤ 1.001 or ≥ 1.020. There were some urine specimens in which one of the measured parameters (*i.e.*, creatinine or specific gravity) met or exceeded the individual criteria, but not both.

Our extensive review of the scientific literature has shown that there were no cases meeting the substituted specimen creatinine/specific gravity criteria in both the medical evaluation population and substance abuse population. Additionally, there were only a small number of either low creatinine <u>or</u> specific gravity test values even in the substance abuse population. These findings, taken together provide the realistic, scientific basis for the selected "substituted" specimen criteria.

Medical Overhydration Studies

Several clinical conditions produce overhydration or polyuria, the production of excessive amounts of urine. The extreme conditions that produce exceedingly dilute urine are described in Table 2, on the next page. Twenty-seven case studies were identified that provided random urine data for creatinine, specific gravity, and/or osmolality. A summary of the medical cases reporting excessive urine production are found in Table 2 in the appendix. In two extreme cases, 19 liters of water were consumed in 6 hours (water intoxication) and 6 liters of water were consumed in "a few" hours (psychogenic polydypsia). The lowest osmolality results from urine specimens collected after consumption of these excessive amounts of water were 142 and 84 mOsm/kg, respectively. Both of these results are comparable to a normal specific gravity (see note below). For those medical case studies where paired creatinine and specific gravity data did exist, no urine specimen was identified in which the urine creatinine concentration was ≤ 5 mg/dL **and** the urine specific gravity was ≤ 1.001 or ≥ 1.020 (*i.e.*, no specimen was identified as "substituted").

Table 2. Medical conditions that result in polyuria.

Condition	Description
Psychogenic polydipsia	Excessive fluid consumption resulting from a disorder in personality, without a demonstrable organic lesion
Water intoxication	Severe overhydration which may result in convulsions and death due to uncorrected hyponatremia and cerebral edema
Diabetes insipidus	The chronic excretion of very large amounts of pale urine of low specific gravity, accompanied by extreme thirst, resulting from inadequate amounts of pituitary antidiuretic hormone (ADH)
Nephrogenic diabetes	The chronic excretion of very large amounts of pale urine of low specific gravity resulting from the inability of the kidneys to respond to ADH
Iatrogenic diabetes	Diabetes introduced by an unfavorable response to a therapeutic intervention

Note: For those cases shown in Table 2 in the appendix where an osmolality measurement was made in the absence of a specific gravity measurement, it should be noted that an osmolality value of 70 mOsm/kg is equal to a specific gravity of 1.002 or greater.

Water Loading Studies

Water loading studies are those in which excessive amounts of water were ingested in an attempt to dilute the urine. Ten water-loading studies were reported that included random urine creatinine and/or specific gravity data. Table 3 in the appendix shows a summary of the water loading studies. In the most significant study, 3.8 to 4.2 liters (about 1 gallon) of fluid were consumed in 4 hours. Analysis of the creatinine concentration and the specific gravity in the urine specimens provided after consumption of this large amount of fluid did not produce any specimens defined as "substituted" (*i.e.*, urine creatinine concentration ≤ 5 mg/dL **and** urine specific gravity ≤ 1.001 or ≥ 1.020). In those studies where paired creatinine and specific gravity data were reported, in no case was the "substituted" criteria achieved; that is, no specimen was identified in which the urine creatinine concentration was ≤ 5 mg/dL **and** the urine specific gravity was ≤ 1.001 or ≥ 1.020. Creatinine or specific gravity values were individually low in a few cases.

Regulatory Actions

The NLCP published PD #35 for reporting urine specimen validity test results.[2] It addressed adulterated and diluted urine specimens and created a new classification known as "substituted" specimens. By definition, a specimen is called "substituted" (*i.e.*, the specimen does not exhibit the clinical signs or characteristics associated with normal human urine) if the urine creatinine concentration is $\leq$ 5 mg/dL <u>and</u> the urine specific gravity is $\leq$ 1.001 or $\geq$ 1.020.

Subsequently, the NLCP published PD #37 (see attachment 2) to provide analytical criteria for laboratories testing Federal and federally regulated specimens when conducting these biochemical tests.[3] To report a specimen as "substituted," at a minimum, creatinine must be measured by at least one quantitative procedure on two different aliquots, both using the specified cutoff of 5 mg/dL. Reported creatinine results must contain one significant decimal place more than that stated in the decision point (*i.e.*, results are reported to the first decimal place). Creatinine values of 5 mg/dL may <u>not</u> be truncated to the nearest whole number.

Also, at a minimum, specific gravity must be determined on one of these aliquots utilizing the specified cutoffs of 1.001 or 1.020. Specific gravity measurements are required to be performed by refractometry and reported to the third decimal place.
Each laboratory must have a written and validated standard operating procedure for performing urine creatinine and specific gravity analyses and is subjected to the same NLCP laboratory inspection protocol as that for evaluating drug testing processes.

Conclusions

In order for a specimen to be reported as substituted, both creatinine and specific gravity must meet defined criteria; that is, urine creatinine $\leq$ 5 mg/dL <u>and</u> urine specific gravity $\leq$ 1.001 or $\geq$ 1.020. This testing requirement provides both an analytical and physiological safeguard. The review of the scientific literature including random clinical studies, medical conditions resulting in severe overhydration or polyuria, and water loading studies confirms that the urine criteria of creatinine $\leq$ 5 mg/dL <u>and</u> urine specific gravity $\leq$ 1.001 or $\geq$ 1.020 represent a specimen condition that is <u>not</u> consistent with normal human urine. In the deductive evaluation of 47 studies, no exception to the criteria defining a "substituted" specimen was reported.

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Appendix tables, references and attachments:

Table 1. Random Clinical Studies

Number of Subjects/Samples	Creatinine Range, (mg/dL)	Specific Gravity Range	Population	Notes	References
14	$\geq$ 10	1.002 – 1.024	Medical		A1
350	172 $\pm$ 81		Medical	All creatinines > 10 mg/dL	A1
50	1.1 - 29	1.001 – 1.084	Drug	No paired data	A2
176	1.1 - 361		Drug		A3
10	183 $\pm$ 85		Medical		A4
9	18 - 532	1.002 – 1.036	Drug	N = 1206	A5
1601		1.000 – 1.055	Drug	0.37% in 1.000 – 1.005 range	A6
423		1.001 – 1.040	Drug	10% in 1.001 – 1.010 range	A7
37	20 - 477		Medical		A8
67	18 - 200		Medical		A9
7	7 - 318	1.001 – 1.029	Drug		A10
6	6 - 360		Drug	N = 955	A11

Table 2. Medical Polyuria Case Studies

Number of Subjects	Condition	Creatinine (mg/dL)	Specific Gravity	Osmolality, (mOsm/kg)	Notes	References
11	Psychogenic Polydipsia		1.002 – 1.024	45 - 530		C1
1	Diabetes Insipidis		1.003	106	12 – 15 L/d	C2
1	Diabetes Insipidis		1.007	296	8.5 L/d	C2
1	Psychogenic Polydipsia			84	> 6 L in "few" h	C3
1	Water Intoxication			237	6 L/d	C4
1	Water Intoxication			142	19 L/6 h	C5
1	Water Intoxication			78	1.44 L ingestion Seizures, coma	C6
1	Diabetes Insipidis	13	1.005	54	4 – 6 L/d	C7
10	Psychogenic Polydipsia	4 - 185	1.000 – 1.017		No paired data	C8
3	Polydipsia			144 $\pm$23		C9
1	Iatrogenic Polydipsia			313	15 – 18 L/d	C10
14	Polydipsia			122 $\pm$66 112 $\pm$57		C11
10	Polydipsia			> 50	20 mL/kg water load in 10 min	C12
1	Psychogenic Polydipsia			154		C13

Number of Subjects	Condition	Creatinine (mg/dL)	Specific Gravity	Osmolality, (mOsm/kg)	Notes	References
1	Psychogenic Polydipsia			141		C14
1	Water Intoxication		1.000	80		C15
1	Water Intoxication			55		C16
3	Water Intoxication		1.000 - 1.002	131 - 590		C17
1	Water Intoxication			87		C18
1	Water Intoxication			203	Ingested 3 L/3 h	C19
1	Water Intoxication		1.000		Ingested 24 L/10 h	C20
4	Psychogenic Polydipsia			143 - 342		C21
2	Water Intoxication		1.001 – 1.006			C22
8	Psychogenic Polydipsia		1.001 – 1.010	56 - 176	Void 5 – 19 L/d	C23
1	Water Intoxication			50 - 60	Void 11 – 17 L/d	C24
11	Diabetes Insipidus			100 - 200		C25
10	Psychogenic Polydipsia			225 - 325		C25
20	Diabetes Insipidus			83 - 303	Void 5 – 12 L/d	C26
4	Nephrogenic Diabetes			64 - 190		C27

Table 3. Water Loading Studies

Number of Subjects	Dose	Creatinine Range, (mg/dL)	Specific Gravity Range	Pairs	Notes	References
6	4 mL/kg over 10 h		1.012 $\pm$0.002	No creatinine data	Osmolality: 295 $\pm$ 69 mOsm/kg	B1
1	1.2 L/1 h 0.1L/30 min 1.4 L/75 min	32 - 157	1.004 – 1.014	Lowest pair: 32 creatinine 1.005 SG	Lowest creatinine: 32 mg/dL	B2
6	1.0 – 2.0 L /4 h	$\geq$ 30	1.003 – 1.010			B3
7	3.8 – 4.2 L/4 h	4 - 266	1.000 – 1.030	Lowest pairs: (4 : 1.003) (5 : 1.003)	SG $\leq$ 1.001 paired with 8 – 12 mg/dL creatinines	B4
2	3.4 - 3.8 L/4 h		1.000	No creatinine data	Only value claimed	B5
23	0.5 L/15 min	8 - 257			Osmolality: 69 – 1075 mOsm/kg	B6
23	1.0 L/15 min	7 - 257			Osmolality: 45 – 996 mOsm/kg	B6
20	0.8, 1.0 and 1.5 L/BSA (m^2)/d		1.025 (0.003) (0.8 L/BSA) 1.022(0.005) (1.0 L/BSA) 1.015(1.010) (1.2 L/BSA)			B7
8	20 mL/kg				Osmolality: 32 – 95 mOsm/kg	B8
9	5.6 $\pm$1.8 L/21 h		1.005 – 1.025		Osmolality: 200 – 850 mOsm/kg	B9
8	2.6 L fluids / 2 h post exercise				Osmolality range 1 h post ingestion: 120– 350 mOsm/kg	

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ATTACHMENT #1
NLCP PROGRAM DOCUMENT #35

September 28, 1998

NOTICE TO HHS CERTIFIED AND APPLICANT LABORATORIES

Subject: Guidance for Reporting Specimen Validity Test Results

The Mandatory Guidelines for Federal Workplace Drug Testing Programs published in the **Federal Register** on June 9, 1994 (59 FR 29908) and the Department of Transportation (DOT) regulations (49 CFR Part 40) applicable to DOT federally regulated programs permit laboratories to conduct additional tests to determine the validity of a specimen. To ensure maximum consistency, the following guidance is provided for all laboratories in determining the validity of a specimen. We have consulted with the Department of Transportation. It agrees with these procedures and definitions and recommends that such procedures be followed for its federally regulated programs.

A. Single and/or Primary (Bottle A) Specimens

1. Guidance

a. A laboratory may determine for each specimen (i.e., from either a single specimen collection or the primary specimen (Bottle A) from a split specimen collection) the nitrite concentration, creatinine concentration, specific gravity, and pH. These tests shall follow scientifically suitable methods and produce results which are accurately quantified.

b. When a laboratory suspects the presence of an interfering substance/adulterant that could make a specimen unsuitable for testing and the laboratory is unable to identify the interfering substance/ adulterant (e.g., glutaraldehyde, surfactant, bleach), the laboratory may send the specimen to another HHS certified laboratory that has the capability of conducting scientifically suitable validity tests to identify the interfering substance/adulterant.

c. A laboratory shall make every effort to conserve the specimen volume for possible future testing.

2. Definitions

Based on information gathered from a review of current clinical and forensic toxicology literature and recommendations made by the Substance Abuse and Mental Health Services Administration's Drug Testing Advisory Board, a specimen is defined to be:

a. *Dilute* if the creatinine is < 20 mg/dL and the specific gravity is < 1.003, unless the criteria for a *substituted specimen* are met.

b. *Substituted* (i.e., the specimen does not exhibit the clinical signs or characteristics associated with normal human urine) if the creatinine concentration is $\leq$ 5 mg/dL and the specific gravity is $\leq$ 1.001 or $\geq$ 1.020.

c. *Adulterated* if the nitrite concentration is $\geq$ 500 μg/mL.

d. *Adulterated* if the pH is $\leq$ 3 or $\geq$ 11.

e. *Adulterated* if an exogenous substance (i.e., a substance which is not a normal constituent of urine) or an endogenous substance at a higher concentration than normal physiological concentration is present in the specimen.

3. Reporting Results

The Federal custody and control form (CCF) requires laboratories to report drug test results as either Negative, Positive (for a specific drug), or Test Not Performed. Additionally, the laboratory must include an appropriate comment on the "Remarks" line in Step 7 on the CCF when the specimen is dilute, adulterated, substituted, or not tested for drugs (e.g., presence of a fatal flaw or uncorrected flaw). If the additional comments cannot be fully described on the "Remarks" line, the laboratory may attach a separate sheet describing the problem, and reference the attachment on the "Remarks" line.

Note: NLCP Program Document #009 (dated October 10, 1991) and DOT memorandum (dated June 1, 1992) titled "Operating Guidance for DOT

Mandated Drug Testing Programs" provide recommendations for rejecting specimens for testing if procedural errors occur.

The following guidance is provided to report a specimen as Negative, Positive, or Test Not Performed:

Negative. The "Negative" box in Step 7 on the CCF is checked when a negative drug test result is obtained on the initial test or on the confirmatory test. If the specimen is also dilute, the laboratory includes the following statement on the "Remarks" line: "Dilute Specimen."

Note: A negative drug test result is __not__ reported when the specimen has been determined to be adulterated or substituted.

Positive. The "Positive" and the specific drug/drug metabolite(s) boxes in Step 7 on the CCF are checked when a positive drug test result is obtained on an initial test and a confirmatory test. If the specimen is also dilute, the laboratory includes the following statement on the "Remarks" line: "Dilute Specimen."

Note: A positive drug test result is __not__ reported when the specimen has been determined to be adulterated or substituted; however, the laboratory may conduct and complete the confirmatory test.

Test Not Performed. The "Test Not Performed" box is checked in Step 7 on the CCF if the specimen is (1) not tested because of a fatal flaw (e.g., broken seal; specimen ID numbers do not match), (2) not tested because of an uncorrected flaw (e.g., a collector's signature was omitted and a signed statement is not received to correct the error), (3) unsuitable for testing or contains an unidentified interferant because a valid drug test result cannot be obtained, (4) adulterated, or (5) substituted.

Note: The "Test Not Performed" box is checked regardless of whether there is a negative or positive drug test result if a specimen has been determined to be adulterated or substituted.

If the "Test Not Performed" box in Step 7 on the CCF is checked, one of the following statements is to be included on the "Remarks" line:

1. "Fatal Flaw, ________" (with the flaw stated)
2. "Uncorrected Flaw, ________" (with the flaw stated)
3. "Specimen Unsuitable: Cannot obtain valid drug test result"

4a. "Specimen Adulterated: Nitrite is too high"
4b. "Specimen Adulterated: pH is too high (or too low)"
4c. "Specimen Adulterated: Presence of ________ (specify) detected"
5. "Specimen Substituted: Not consistent with normal human urine"

Note: The quantitative results for validity tests (e.g., nitrite concentration, creatinine concentration, actual specific gravity, or actual pH) may not be routinely reported to the MRO, but may be provided to the MRO upon request on a case by case basis.

B. Split (Bottle B) Specimens

1. Guidance

a. When a donor requests, through the MRO, to have the split (Bottle B) specimen tested, a second laboratory (Laboratory B) tests the split specimen for the drug/drug metabolite detected in the primary specimen.

b. If Laboratory B is unable to reconfirm the presence of the drug/drug metabolite that was reported positive in the primary specimen by Laboratory A, Laboratory B must conduct validity tests in an attempt to determine the reason for being unable to reconfirm the presence of the drug/drug metabolite. Laboratory B should conduct the same validity tests as it would conduct on a primary (Bottle A) specimen.

Note: Occasionally, Laboratory B is unable to reconfirm the presence of a drug/drug metabolite (i.e., the confirmatory test results fail to satisfy the criteria established by Laboratory B to report a positive test result) but the laboratory believes that the drug/drug metabolite is present. In this case, Laboratory B may decide to continue testing the split specimen in an attempt to get a valid confirmatory test result. If it appears that Laboratory B may possibly use the entire split specimen in an attempt to get a valid confirmatory test result, Laboratory B must contact the MRO and explain the problem. Laboratory B and the MRO must decide if the remaining amount of the split specimen should be sent to a

Laboratory C for the confirmatory test. If the decision is made to use a Laboratory C, Laboratory B sends the split specimen using chain of custody procedures to Laboratory C without reporting a result to the MRO.

c. If Laboratory B is unable to conduct the validity tests, Laboratory B must send the split (Bottle B) specimen and Copy 3 of the Federal custody and control form using chain of custody procedures to a third laboratory (Laboratory C) that has the capability to conduct the validity tests. If the validity tests conducted by Laboratory C do not determine the reason for being unable to reconfirm the presence of the drug/drug metabolite in the split specimen, Laboratory C must test the split (Bottle B) specimen for the drug/metabolite found in Bottle A by Laboratory A.

2. Definitions

Same definitions as in section A.2 of this Program Document.

3. Reporting Split Specimen Results

The CCF requires laboratories to report split (Bottle B) specimen test results as either Reconfirmed (notating the specific drug), Failed to Reconfirm, or Test Not Performed. Additionally, the laboratory must include an appropriate comment on the "Remarks" line in Step 7 on Copy 3 of the CCF if it finds that the specimen is adulterated or substituted, or when a drug test was not performed.

The following guidance is provided to report a specimen as Reconfirmed, Failed to Reconfirm, or Test Not Performed:

Reconfirmed. The "Reconfirmed" and the specific drug/drug metabolite boxes are checked in Step 7 on Copy 3 when the laboratory confirms the presence of the drug/drug metabolite that was reported positive in the primary specimen.

Failed to Reconfirm. The "Failed to Reconfirm" box in Step 7 on Copy 3 of the CCF is checked if (1) the drug/drug metabolite is not detected, (2) the specimen is adulterated, or (3) the specimen is substituted.

If the "Failed to Reconfirm" box is checked, one of the following statements must be included on the "Remarks" line:

1. "Drug/Drug metabolite not detected"
2a. "Specimen Adulterated: Nitrite is too high"
2b. "Specimen Adulterated: pH is too high (or too low)"
2c. "Specimen Adulterated: Presence of ________ (specify) detected"
3. "Specimen Substituted: Not consistent with normal human urine"

Test Not Performed. The "Test Not Performed" box in Step 7 on Copy 3 of the CCF is checked if (1) the specimen is not tested for drugs or (2) the testing could not be completed successfully.

If the "Test Not Performed" box is checked, one of the following statements must be included on the "Remarks" line:

1a. "Fatal Flaw, ________ (with the flaw stated)"
1b. "Uncorrected flaw, _________ (with the flaw stated)"
2a. "Specimen Unsuitable: Cannot obtain valid confirmatory test result"
2b. "Insufficient specimen volume to complete testing"

This Program Document supersedes and replaces PD #033, and should be used in conjunction with DOT memorandum ("MRO Guidance for Interpreting Specimen Validity Test Results") dated September 28, 1998.

If you have any questions regarding this guidance, please contact my staff at (301) 443-6014.

Robert L. Stephenson II, M.P.H.
Director (Acting)
Division of Workplace Programs

ATTACHMENT # 2
NLCP PROGRAM DOCUMENT #37

July 28, 1999

NOTICE TO HHS CERTIFIED LABORATORIES AND INSPECTORS

Subject: Specimen Validity Testing

The Department of Health and Human Services' (HHS) Mandatory Guidelines for Federal Workplace Drug Testing Programs require laboratories to test urine specimens for only those drugs included in agency drug-free workplace plans. Additionally, the Guidelines permit laboratories to conduct other tests to determine the validity of the specimen.

Certified laboratories reported that the number of adulterated, substituted, and diluted specimens have been increasing. HHS and the Department of Transportation (DOT) began a process utilizing the HHS Substance Abuse and Mental Health Services Administration's Drug Testing Advisory Board (DTAB) to establish a policy for testing, reporting, and interpreting validity test results for specimens tested under federally regulated programs. A team of program staff and consultants determined the normal ranges for the routine clinical measurements that could be conducted on urine specimens and selected levels that were outside the normal range for each clinical measurement. As a result of this effort, National Laboratory Certification Program (NLCP) Program Document #35 was issued on September 28, 1998, to provide guidance to laboratories in determining the validity of urine specimens.

General Guidance/Criteria

Specimen validity testing is the evaluation of the specimen to determine if it is consistent with normal human urine. Validity testing is used to determine if adulterants or foreign substances were added to the urine specimen or if the specimen was substituted. Specimen validity can be determined by establishing parameters that are consistent with normal human urine and/or by testing for the presence of an abnormal or foreign substance in the urine. Specimen validity testing may be conducted on Bottle A and *must* be conducted on Bottle B if Bottle B fails to reconfirm for the requested drug/analyte. Specimen validity tests *may* include, but are not limited to, tests for creatinine concentration, specific gravity, pH, nitrite concentration, pyridine, glutaraldehyde, bleach, and soap. These tests must be performed using methods that are validated by the laboratory.

Specimen validity testing shall be conducted utilizing the following criteria:

1. For dilute specimens, at a minimum, creatinine and specific gravity must be measured by quantitative procedures at a cutoff of 20 mg/dL and 1.003, respectively.

2. For substituted specimens, at a minimum, creatinine must be measured by at least one quantitative procedure on two different aliquots both utilizing the specified cutoff of 5 mg/dL. At a minimum, specific gravity must be performed on one of these aliquots utilizing the specified cutoffs of 1.001 or 1.020.

3. For adulterated specimens, concerning pH and nitrites, at a minimum, two procedures must be performed for pH and nitrites. One procedure must be quantitative and utilize the specified cutoff. The second procedure may be qualitative, must be at least as sensitive as the quantitative procedure, and must be performed on a separate aliquot.

4. For adulterant analytes without a specified cutoff (e.g., glutaraldehyde, bleach, surfactant), at least one procedure must be performed on two separate aliquots.

5. All specimen validity testing methods must be characterized by demonstrating precision and accuracy. Where cutoffs are specified, the limit of quantitation (LOQ) and linearity must be determined. The limit of detection (LOD) must be experimentally determined for qualitative methods.

6. All methods used to characterize and validate these tests must be documented in the laboratory's SOP.

<u>Specific Issues/Comments</u>

Issue 1: Is a certified laboratory required to implement validity testing?

Comment: Currently, validity testing is optional. If a laboratory chooses to conduct validity tests, the laboratory must use the definitions provided in PD35 to report results for specimens that are dilute/adulterated/substituted.

Issue 2: A laboratory may send a specimen to another HHS certified laboratory that has the capability of identifying the presence of an interfering substance/adulterant. Does the laboratory send an aliquot or the entire specimen to the other certified laboratory?

Comment: If a certified laboratory suspects the presence of an interfering substance/adulterant that it is unable to identify and decides to send the specimen to another laboratory, it must send the entire specimen to the other certified laboratory. The selection of the other laboratory must be made in coordination with the MRO. When transferring a single specimen bottle/split specimen bottles to another certified laboratory, the single specimen/primary (Bottle A) specimen must be resealed. All specimen bottles and chain of custody forms received from the collection site must accompany the specimen bottle(s) to the other laboratory (i.e., copies 1, 2, and 3 of the CCF and all internal chain of custody documents). The primary laboratory should retain copies of all original documents sent to the second laboratory. When the transfer occurs, the primary laboratory must not report any result to the Medical Review Officer (MRO).

Note: The process of transferring specimens to another laboratory may add several days to the reporting time. It is strongly recommended that specimens be kept refrigerated during the transfer to the other laboratory to minimize degradation or changes caused by any adulterants or interfering substances.

Issue 3: When a specimen is sent to a second laboratory, what results does the second laboratory report to the MRO?

Comment: The second laboratory reports results of its drug testing and/or validity testing to the MRO in accordance with PD35. The original laboratory must not report any results to the MRO.

Issue 4: Is a certified laboratory required to accept and test specimens sent to it by another laboratory without prior notification?

Comment: No. Although the NLCP requires every certified laboratory to have the capability to perform reconfirmation testing, a certified laboratory is not required to accept specimens for reconfirmation testing or to accept specimens for validity testing unless this has been agreed upon *before* the specimens are sent by the first laboratory. Each laboratory should establish prior agreements with a few selected laboratories to ensure that transfers of specimens are handled expeditiously. The transfer of specimens must be made in coordination with the MRO. If a laboratory chooses not to accept a specimen for retesting, it must contact the sender and make arrangements to forward the specimen to an alternate laboratory.

Issue 5: How does a laboratory interpret quantitative specimen validity results?

Comment: Truncating a quantitative value has been acceptable with "≥", ">", and "<" decision points or cutoffs. However, truncating a quantitative value is not acceptable with "≤" decision points or cutoffs. In "≤" scenarios, truncating would change the result from acceptable to unacceptable (e.g., truncating a pH reading of 3.2 to 3 or a creatinine of 5.4 mg/dL to 5 mg/dL). Values from tests for creatinine (≤5 mg/dL) or pH (≤3) should contain one significant decimal place more than that specified in the stated decision point. For specific gravity (≤ 1.001), the method must measure to the third (3rd) decimal place. This will require refractometry because spectrophotometric and "paper/stick" procedures are not sensitive enough to accurately discriminate in that range.

Issue 6: What are the minimum quality control requirements for conducting a specimen validity test?

Comment: There should be at least one control in the "acceptable" range and one control in the "unacceptable" range analyzed with each batch of validity test specimens. Assays that have more than one decision point (i.e., creatinine, specific gravity, and pH) require more than one control in the unacceptable range: creatinine <20 mg/dL and ≤5 mg/dL; specific gravity ≥1.020, < 1.003, and ≤1.001; and pH ≤3 and ≥11. Controls should be prepared in an appropriate urine matrix and validated according to the laboratory's standard operating procedure (SOP) manual. In the case of pH controls, an appropriate buffer matrix may be used and the controls validated according to the laboratory's SOP manual. All controls must be validated prior to use.

Issue 7: Many laboratories have observed a significant increase in specimens which have a creatinine of ≤5 mg/dL, but have a specific gravity that is acceptable between 1.003 and 1.019. The specimens appear to be saline. These do not fit the definitions of "dilute" or "substituted" as stated in PD35. How are these specimens to be reported?

Comment: For specimens of this type, the laboratory should provide a "Specimen Unsuitable: Unable to Obtain Valid Drug Test Results" comment in block 7 of the CCF ***without*** reporting a "negative" drug test result.

Issue 8: Is more than one comment allowed when multiple adulterants are identified and the specimen is reported "Test Not Performed" or "Failed to Reconfirm"?

Comment: Although it is sufficient to provide only one comment listed in PD35 under "Test Not Performed" or "Failed to Reconfirm" to support an "adulterated" or "substituted" result, the laboratory may provide multiple comments if it has validity test results that require multiple comments.

Issue 9: Some manufacturers of immunoassay test kits have established an acceptable range for the pH of a specimen (e.g., 4.5 - 9). Can a laboratory reject a specimen as "unsuitable for testing" based on pH without determining whether it is adulterated (i.e., $\leq$ 3 or $\geq$ 11)?

Comment: Yes, a laboratory can reject specimens that do not meet its specimen acceptance criteria. Specimen rejection criteria are separate from specimen validity testing. Rejected specimens are reported as "Test Not Performed" with the comment "Specimen Unsuitable: Unable to Obtain Valid Drug Test Results." This comment is appropriate with a number of specimen rejection criteria, such as, the observation of foreign objects, unacceptable coloration, unacceptable viscosity, unacceptable odor, or when the pH indicates that the specimen is outside the recommended pH range established by the immunoassay test kit manufacturer. These criteria are separate from specimen validity testing and are not associated with the definitions of PD35.

Issue 10: Can a laboratory reject a specimen as "unsuitable for testing" based on pH *instead of* reporting it as "adulterated" when pH is $\leq$3 or $\geq$11?

Comment: No, if a laboratory measures pH as a component of its specimen validity testing, it must adhere to the reporting criteria specified in PD 35. Moreover, the procedures utilized must be validated by the laboratory and follow the criteria outlined in paragraph 3. A. of this document.

Issue 11: Some laboratories indicate that assay performance is adversely affected when nitrite is present but <500 μg/mL. Can a laboratory report "unsuitable for testing" when nitrite is <500 μg/mL?

Comment: If the nitrite concentration is <500 μg/mL and the laboratory is unable to obtain a valid confirmatory test result, the laboratory may report "Test Not Performed." In addition, the comment "Specimen Unsuitable: Cannot obtain valid drug test result" must be entered on the comment line indicating that it is the laboratory's belief that the failure to obtain a valid confirmatory test result is caused solely by the presence of nitrite. However, if the laboratory is uncertain that nitrites are the cause for the failure to confirm because there may be an unidentified interfering substance/adulterant in the specimen, the laboratory *may* send the entire specimen to another certified laboratory (see issue 2 above).

Issue 12: Can "Adulterated" take precedence over "Reconfirmed the presence of ..." for a split specimen? For example, if a split specimen is positive for nitrite, is the split specimen reported "adulterated" even if the laboratory has reconfirmed an analyte that may or may not be affected by nitrite?

Comment: No. Since the primary (Bottle A) specimen was reported "positive" for a specific drug, laboratory B is always required to conduct the confirmatory test for that drug and to report it as "reconfirmed" if it reconfirms the analyte. If laboratory B is unable to reconfirm the presence of the drug, it must perform specimen validity testing to attempt to determine the reason for being unable to reconfirm the presence of the drug (PD35, Paragraph B.1.b).

Issue 13: The primary specimen (Bottle A) is reported substituted or adulterated. What must the laboratory do with Bottle B?

Comment: When a primary specimen (Bottle A) is reported adulterated or substituted, the laboratory must retain both Bottle A and Bottle B for a minimum of 12 months.

If you have any questions regarding these issues or comments, please contact my staff at (301) 443-6014.

Robert L. Stephenson II, M.P.H.
Director (Acting)
Division of Workplace Programs

Correlation Coefficient: 0.999
Regression Equation: AU5200 = (AU5000 x 0.994) + 0.02

Sensitivity:
The typical change in absorbance for 1 mg/dL of creatinine is 10.4 mA per minute.

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OLYMPUS®

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INTENDED USE

Reagent for the quantitative determination of creatinine concentrations in human serum on the Olympus AU5000® and AU5200® chemistry analyzers.

SUMMARY

Creatinine is an end product of glycine and arginine metabolism. Serum creatinine measurements are useful in the evaluation of renal dysfunction.

METHODOLOGY

The Olympus creatinine procedure for use on the AU5000 and AU5200 analyzers is a kinetic modification of the Jaffe procedure.[1] Creatinine reacts with alkaline picrate to form a red-colored complex. The rate of change in absorbance is measured bichromatically at 520/660 nm and is proportional to the creatinine concentration in the sample.

REAGENTS

Reactive components in the test:

Picric acid	2.5 mmol/L
Sodium hydroxide	214 mmol/L

Also contains preservatives.

D.Ex 14

Precautions:

1. For *in vitro* diagnostic use.

2. Creatinine R1 reagent contains picric acid which is poisonous. Dry picric acid explodes if rapidly heated or subjected to percussion. Dilute any spills with water and wipe up immediately. The reagent will also stain skin and clothing. In case of external contact, flush with copious amounts of water. For ingestion or eye contact, seek medical attention.

3. Creatinine R2 reagent is corrosive. DO NOT PIPETTE BY MOUTH. Avoid contact with skin or eyes. In case of external contact, flush with copious amounts of water. For ingestion, seek immediate medical attention.

Preparation:
Both R1 and R2 creatinine reagents are ready for use as supplied.

Storage & Stability:

1. The unopened reagents are stable until the expiration date when stored at 2-25°C.

2. The opened and working reagents are stable for 14 days when stored in the ambient compartment of the AU5000 and AU5200 analyzers.

3. Working reagent should be kept covered.

Indications Of Deterioration:
Turbidity in the unopened liquids and working reagent may indicate decomposition and warrant discontinuance of use.

SPECIMEN COLLECTION & PREPARATION
Clear, unhemolyzed serum obtained after a 12 to 14 hour fast is the recommended sample[2]. Separate serum from blood cells as soon as possible. No special additives or preservatives are required.

Sample Storage:
Serum creatinine is stable for approximately 7 days when stored at 15-25°C.[3]

Interfering Substances:
Results of studies conducted[4] show that the following substances interfere with this creatinine procedure:

Protein: No interference from protein up to 7.0 g/dL
Lipemia: No interference from triglyceride up to 3000 mg/dL
Bilirubin: No interference from bilirubin up to 10 mg/dL
Hemolysis: No interference from hemoglobin up to 500 mg/dL

Drugs and other endogenous substances may affect creatinine determinations. Refer to Young[5] for a compilation of reported interferences with this test.

PROCEDURE
Materials Provided:
Olympus AU5000/AU5200 creatinine reagent

Materials Required But Not Provided:
Olympus AU5000 or AU5200 chemistry analyzer
Olympus sample cups (Catalog No. AR0063)
Olympus calibrator (Catalog No. DR0060)

Suggested Analytical Parameters:
Refer to the Methodology Section located in the respective analyzer's Operator's Manual.

Stability Of Final Reaction Mixture:
Both the AU5000 and AU5200 automatically compute each determination at the same time interval at 37°C.

Calibration:
The calibration frequency for this procedure is daily. Calibration of this creatinine procedure is accomplished by Olympus calibrator material which is traceable to the National Institutes of Standards and Technology (NIST) Standard Reference Material (SRM) 909a-2.

Recalibration of this procedure is required when a reagent lot number has changed and there is an observed shift in control values, if a critical part of the analyzer is replaced or, if a major preventative maintenance procedure was performed on the analyzer.

Quality Control:
Olympus Level I and Level II control sera (Catalog Nos. DR0055 and DR0056) should be analyzed routinely with each group of unknown samples.

Results:
Results in mg/dL at 37°C will be automatically printed for each sample assayed.

LIMITATIONS OF THE PROCEDURE
The Olympus AU5000/AU5200 creatinine procedure is linear to 30.0 mg/dL. Samples exceeding the dynamic range of the assay should be diluted with isotonic saline and reassayed. The results obtained must be multiplied by the dilution factor to obtain the correct concentration for the undiluted sample.

EXPECTED VALUES
Adult 0.8 - 1.6 mg/dL

This reference range was determined from 200 New York blood donors (data on file). Expected values may vary with age, sex, diet and geographical location. Good laboratory practice dictates that each laboratory determine its own expected values.

SPECIFIC PERFORMANCE CHARACTERISTICS
The following data was obtained using the Olympus AU5000/AU5200 creatinine reagents on the respective analyzers according to established procedures.

Precision:
Estimates of precision, based on NCCLS recommendations[6], are consistent with typical performance. Assays of control sera products were performed and the data reduced following the NCCLS guidelines above.

AU5000:

N=50	Within Run		Total	
X	SD	CV%	SD	CV%
1.6 mg/dL	0.031	1.98	0.042	2.64
7.5 mg/dL	0.094	1.26	0.158	2.10

AU5200:

N=50	Within Run		Total	
X	SD	CV%	SD	CV%
1.8 mg/dL	0.046	2.60	0.050	2.90
5.5 mg/dL	0.040	0.64	0.040	0.64

Method Comparison:
A comparison of this Olympus creatinine method (Method 1) versus another Olympus creatinine method (Method 2) was run on an AU5200 utilizing 150 patient serum samples. The resulting data is as follows:

Correlation Coefficient: 0.998
Regression Equation: Method 1 = (Method 2 x 1.133) - 0.096

A comparison of this Olympus creatinine method was run on the AU5200 versus the AU5000 using 150 patient samples. Results were as follows: